VOLUME 63 • JANUARY 1957 • NUMBER 1

PATHOLOGY

A Periodical Devoted to General and Experimental Pathology

AMERICAN MEDICAL ASSOCIATION PUBLICATION

TABLE OF CONTENTS

VOLUME 63 JANUARY 1957 NUMBER 1

ORIGINAL ARTICLES

REGULAR DEPARTMENTS

A. M. A.
ARCHIVES of PATHOLOGY

Also the Official Organ of the AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

VOLUME 63 JANUARY 1957 NUMBER 1

SUBSCRIPTION RATES

Price per annum in advance, including postage: Domestic, $10.00. Canadian, $10.50. Foreign, $11.50. Price to students, interns, and residents, $6.00 in U. S. & possessions.

Single copies of this and previous calendar year, $1.00 each. Back issues older than two years are available through Walter J. Johnson, Inc., 111 Fifth Avenue, New York 3. Future reprints of back issues will be available through Johnson Reprint Corporation, 111 Fifth Avenue, New York 3.

Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

AMERICAN MEDICAL ASSOCIATION Publication

Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee. Change of Address: Notice to the circulation office should state whether or not change is permanent and should include the old address. Six weeks' notice is required to effect a change of address. Second-class mail privileges authorized at Nashville, Tenn., Aug. 6, 1956.

Paragon Tray Drawer Cabinet

Compact

Low Cost

FOR FILING
MICROSCOPIC SLIDES 3 x 1″
KODACHROME TRANSPARENCIES
2 x 2″ SLIDES
LANTERN SLIDES
(up to 3¼ x 4¼)
PETROGRAPHIC SLIDES

When you purchase a
PARAGON TRAY DRAWER CABINET
YOU PURCHASE FILING SPACE ONLY
NO WASTE SPACE-EVERY INCH USED

U. S. Pat. No. 2,202,047
C101—Tray Drawer Cabinet for 3 x 1 Micro Slides
Capacity 4500—18¾ x 15¾ x 4¾

All Paragon Tray Drawer Cabinets are manufactured in standard sizes so that any number of sections may be interlocked to form one cabinet to accommodate any number of varied slides. The dimensions of the different cabinets are the same as to length and width, varying only in height. The cabinet formed by interlocking may be 18¾ x 15¾; 18¾ x 11 or 18¾ x 5 or it may be a pyramid with the sections varying in width.

C221—Capacity 1500 Slides—18¾ x 11 x 3⅞
For Filing KODACHROME TRANSPARENCIES and 2 x 2″ SLIDES

SPECIFICATIONS: All Paragon Tray Drawer Cabinets are made of reinforced steel construction, olive green finish. Interlocking device enables several units to be joined into one. Each sectional unit contains removable drawers with hand grip in front and rear. Interlocking steel base obtainable whenever required. **Constructed according to rigid specifications—not merely adapted.**

Address your orders and inquiries to Dept. P.

Manufactured Exclusively by

PARAGON C. & C. CO., Inc. • 2540 Belmont Ave., New York 58, N.Y.

New Cover Design

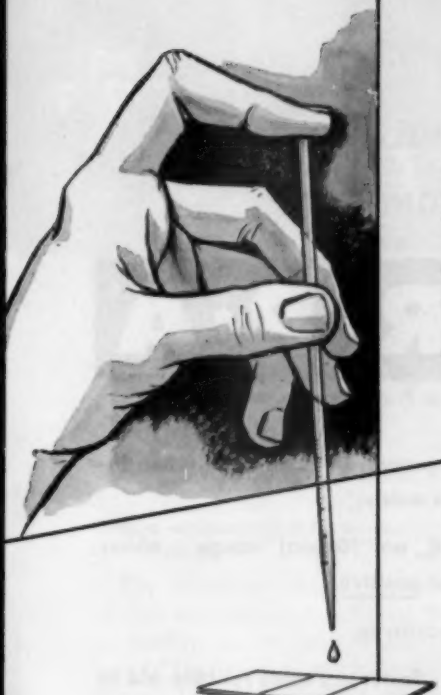
With this issue, the A. M. A. ARCHIVES OF PATHOLOGY presents a new cover design and a slight modification of page format.

Two elements contribute to an attractive cover—simplicity and cleanliness. We believe that we have obtained the two primary objectives necessary in a cover design of this nature: namely, that it is attractive and that it conveys the subjective feeling of the unit which it represents, as well as legibility, which is important in this case because of the contents listing involved. This cover is fluid enough to attractively accommodate varying lengths of contents listing. By the use of a simple line or block treatment, and by placing the contents upon a white background, we gain the maximum contrast possible, therefore, greater legibility.

The use of the seal has several functions: Being a circle in design, it relieves to an extent the over-all use of lines, squares, and rectangles; it stands as a symbol for the many years of dedicated service by an organization of the American Medical Association's stature in the advancement of knowledge in specialized fields, thus adding immeasurably to the effectiveness of the design.

The change in page format is confined to the title, subtitle, and authors' names. The change from a Coronet Bold type face to Bodoni Bold will eliminate the difficulty encountered when reading a formula or an abbreviation in script capitals. The use of Antique Italic for subtitles and Spartan Bold for the authors creates a desirable distinction between these parts. The arrangement realizes a saving in space.

This new cover is a development of an idea. It is not the result of a sudden thought. First, a suggestion was presented which was nothing more than a different arrangement of familiar elements. Then followed the collection of reactions, suggestions, and additional experimentation in search for the inspiration. All of the separate bits of information gathered were thoroughly digested, and the relationship between elements was established. The result is the crystallization of the idea. In following this procedure, our readers and editors have contributed immeasurably to the end product. Their cooperation means a new design of lasting quality.



notes from a MICROSCOPIST'S NOTEBOOK

NATIONAL® BIOLOGICAL STAINS for Cytoplasmic Staining

Counterstaining the cytoplasm a contrasting color to the stained nuclei to permit examination of tissue cells in their entirety has made this group of stains important in histologic work and an important part of National's comprehensive line of Biological Stains.

Acid Fuchsin, Eosin B, Eosin Y, Erythrosin B, Orange G, and Phloxine B are frequently used in combination with other nuclear stains. The wide range of colors available affords ample choice of contrasting colors.

Likewise in trichrome or one-step trichrome stains, there are multiple choices of cytoplasmic and nuclear stains to accomplish sharp differentiation. Cytoplasmic stains are also valuable as counterstains in demonstrating fungi, mucin, elastic fibers, reticulum or bacteria.

For your convenience in ordering, we list the National Commission Certified Biological Stains most frequently specified for Cytoplasmic Staining:

#402—Acid Fuchsin
#426—Aniline Blue WS
#516—Eosin Y (W. & A. Sol.)
#537—Fast Green F.C.F.
#594—Light Green SF Yellowish
#690—Orange G
#602—Phloxine B

NATIONAL BIOLOGICAL STAINS and INDICATORS

PRODUCTS OF THE PHARMACEUTICAL LABORATORIES
NATIONAL ANILINE DIVISION
ALLIED CHEMICAL & DYE CORPORATION
40 RECTOR STREET, NEW YORK 6, N. Y.

1957 Silver Anniversary of the American Society of Medical Technologists

BRING YOUR PATIENT'S HIDDEN INFLAMMATION TO LIGHT WITH

C·R·P·A®

(C-reactive Protein Antiserum, Schieffelin)

- **C-Reactive protein in serum only when inflammation exists.**
- **Unlike E.S.R., no "Normal" range...either negative or positive.**
- **No false positives.**
- **Simpler . . . faster . . . more reliable aid to diagnosis.**
- **Quantity of precipitate reflects severity of condition . . . Precipitate diminishes as therapy reduces inflammation.**

Both venous blood and blood obtained by the "finger tip technique" (punctured as for blood count) can be used with equally reliable results. To make the test procedure fast and convenient a new compact C.R.P.A. Test Kit is now available; it contains C.R.P.A., CRP-Positest control solution, capillary tubes, test rack, and illustrated directions.

COMPLETE LITERATURE ON C.R.P.A. IN DETECTION OF RHEUMATIC DISEASES, MYOCARDIAL INFARCTION, AND MANY OTHER DISEASE STATES ON REQUEST.

Supplied:

TEST KIT *(For the complete procedure)*

C.R.P.A. . . . 1 ml. vials (80-110 determinations)

CRP-POSITEST* . . . 0.5 ml. vials
(Standardized test-control solution of C-Reactive Protein)

CAPILLARY TUBE RACK

CAPILLARY TUBES
(Two sizes) . . . 0.8 mm ID – 1.5 mm ID

*Trademark

Schieffelin & Co.

New York 3, N. Y. • Since 1794

Laboratory Products Division

In Canada: William Sofn & Co., Ltd., Montreal 25, Quebec

A.M.A. ARCHIVES OF
PATHOLOGY

The Changing Neuropathologic Picture of Chronic Alcoholism

Prevailing Involvement of the Cere bellar Granular Layer

KARL T. NEUBUERGER, M.D., Denver

The histolopathology of the brain in chronic alcoholics has sustained the interest of workers in the field of neuropathology over a long period of time. An excellent historical sketch of pertinent research has been given recently by Courville.[1] It is worth noting that one group of workers has endeavored to explain the clinical picture of mental deterioration and other symptoms on the basis of cortical changes. Such changes, however, almost always have proved to be rather monotonous and nonspecific. Another group of investigators tried to find more characteristic and perhaps specific changes by examination of extracortical as well as cortical territories. The latter avenue of approach appeared to be more fruitful. The cornerstones in this endeavor were the description of the alterations of "superior hemorrhagic polioencephalitis" by Wernicke,[2] in 1881; the discovery of atrophy and sclerosis of the mammillary bodies by Gudden,[3] in 1896, and the studies of Gamper,[4] in which he showed that the diseased mammillary bodies and other centers in the interbrain were the fulcrum of the pathologic process in chronic alcoholism, especially in Korsakoff's psychosis (1927).

Later studies have indicated that changes in those centers of the interbrain were not pathognomonic of alcoholism. I [5,6] was able to demonstrate similar lesions in patients with gastric cancer and with chronic atrophic gastritis. Work by various authors over the last two decades has furnished convincing evidence to show that nutritional deficiencies are essentially responsible for these changes even in alcoholics.[7]

It has been the experience of authors in this country and abroad that the classical changes have become rare indeed over a number of years. There is no doubt that the clinical syndrome of Wernicke's disease still exists, especially in its acute stages, but now it can be treated successfully. Rupp and Riggs [8] have stated that the number of cases of Wernicke's disease based on necropsy findings had decreased in their material from 42, during 1934 to 1943, to 13, during 1944 to 1953. They felt that the general public had become more "vitamin-conscious" and that alcohol per se was not the prime offender. Many of their cases came from tuberculosis and gynecologic wards, where infection superimposed on poor diet seemed to be the chief factor.

The alcohologenic brain disease described by Marchiafava and Bignami in 1903, which

Submitted for publication July 30, 1956.

Read at the Second International Congress of Neuropathology, London, England, Sept. 1955.

From the Departments of Pathology, University of Colorado School of Medicine, and General Rose Memorial Hospital.

Pathologist, General Rose Memorial Hospital; Professor of Pathology, University of Colorado School of Medicine.

consists of degeneration of the corpus callosum and its radiations, has for a long time been considered a rare occurrence, limited chiefly to elderly men of Italian extraction, who indulged in special brands of crude red wine. However, more recent investigations, notably those of Orlando,[9] Riese and coworkers,[10] and Seitelberger and Berner,[11] have shown that age, sex, nationality, and heredity, as well as the brand of beverage, may be inconsequential in the etiology of this disease.

During the period from 1953 to 1955 my colleagues and I have studied the brains of 42 alcoholics, aged from 30 to 70 years, one-third of whom were women. The material differed to some extent from that on which my previous studies[12] in this field were based. The older material consisted predominantly of patients who had been confined in general and mental hospitals for varying lengths of time, and for whom more or less satisfactory clinical histories were available. The new material was obtained from medicolegal necropsies on known chronic drinkers who had been hospitalized in the terminal stage or were dead upon arrival. Unfortunately, detailed clinical histories were seldom obtained. We felt that comparison of old and new material was justified, since chronic alcoholism was the essential condition in both groups.

In the new group, excessive amounts of alcohol in the blood were found in many instances. Most subjects had a fatty liver, with or without cirrhosis. Some had lobar pneumonia. Evidence of old traumatic brain injury and mild degrees of internal hemorrhagic pachymeningitis were found in isolated cases. Atrophy of the brain, present in less than 50% of the patients, was mild and sometimes was accompanied by edema of the leptomeninges. Our observations appeared to contradict, to some extent, modern clinical impressions and the contention of Courville,[1] that chronic alcoholism is "the most common cause of cerebral cortical atrophy in the 5th and 6th decades of life."

The histologic changes in the cases with cortical cerebral atrophy were accentuated in the middle layers and consisted of the following: thinning of the cortical band; loss of stratification; decrease in the number of neurons with occasional patchy "outfall," nonspecific neuronal degeneration (tigrolysis, chronic cell alteration, blanching, severe cell disease, mild degrees of precocious lipid atrophy); slight plasmatic gliosis, and, sometimes, presence of "naked glial nuclei," consistent with customary findings in diffuse liver disease. (The main site of such nuclei, however, was the dentate nucleus.)

These cerebral lesions as a rule were not very severe and certainly could not be considered to be specific. They could not be distinguished from changes frequently seen in middle-aged people dying from a variety of subacute or chronic conditions. The possible significance of the alterations in conjunction with mental deterioration of chronic drinkers can, of course, not be denied.

The classical picture of Wernicke's disease, with lesions centering around the mammillary bodies, a picture which had been prevailing in our old material, was noted in only two instances. Slight focal demyelination of the corpus callosum was seen in two other cases and appeared to indicate abortive changes of Marchiafava-Bignami disease. It would seem that this condition, which is still believed to be rare, is not too unusual, at least in mild form.

The most impressive changes were found in the cerebellar cortex. They consisted of selective degeneration of the granular layer; this was only rarely accompanied by serious alteration or loss of Purkinje cells, although their distribution occasionally was somewhat irregular. The lesions occurred in 28 cases; in 12 of these (over 28% of the total) the damage was severe enough to lead to complete, or nearly complete, obliteration of the granular layer.

Cerebellar lesions, especially lobular necrosis or atrophy and disintegration of Purkinje cells, have been known for a long time in alcoholics (Stender and Lüthy,[13] Santha,[14] Feyzullaeff and Sukhova[15]), and

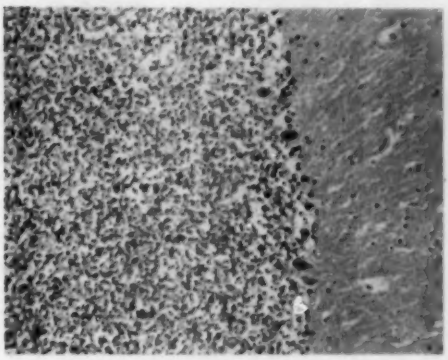


Fig. 1.—Cerebellar cortex with rarefaction of granular layer. Reduced to 62% of mag. × 80.

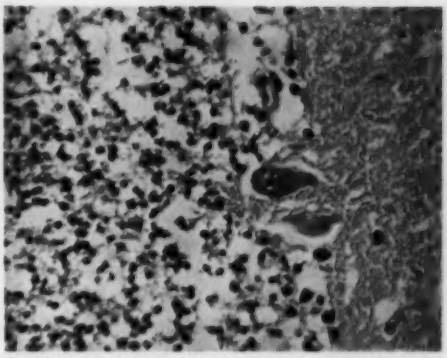


Fig. 2.—Same section as Figure 1, higher magnification. Deformed shrunken nuclei and amorphous interstitial material. Reduced to 62% of mag. × 250.

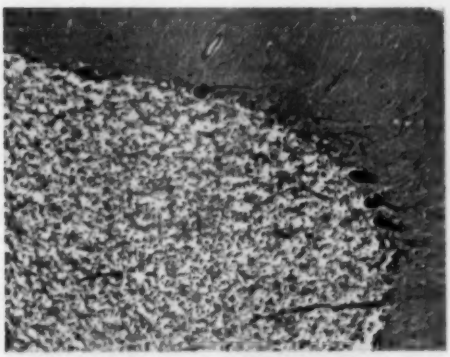


Fig. 3.—Nearly total obliteration of granular layer with preservation of Purkinje cells. Reduced to 62% of mag. × 80.

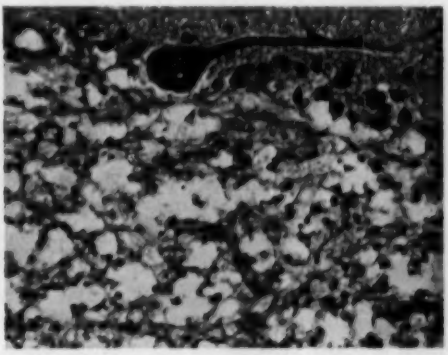


Fig. 4.—Same section as Figure 3, higher magnification: Nuclear debris and coarse vacuolation. Reduced to 62% of mag. × 300.

degeneration of the granular layer has been reported in rare instances as a feature of Wernicke's disease (Meyer [16]). To our knowledge, however, selective degeneration of this layer has not been described as a frequent finding in a larger group of alcoholics. Courville [1] mentioned its occurrence "in some instances."

The lesion was ubiquitous. Upper and lower cerebellar surfaces, tonsils, and vermis were examined routinely in the more recent cases. The vermis, as a rule, was most severely involved, but regional differences were not very impressive.

The granular layer has a tendency to disintegrate rapidly when autolysis sets in. It should be stated, therefore, that autolytic changes did not play a role in our material.

Histologic analysis of these alterations does not require special neurohistologic methods. In fact, the hematoxylin-eosin method affords ample opportunity to study the lesion. Clumping and irregular arrangement of granules, with the presence of eosinophilic amorphous interstitial material, appeared to be the first stage but was difficult to distinguish from the normal. In later stages, the granules showed alterations, and the amount of fuzzy, thready, grainy, or amorphous substance was increased. In the final, or severest, stages, we observed a coarsely vacuolar, almost unnucleated eosinophilic meshwork. Stains for neurofibrils at this stage showed degeneration of climbing and mossy fibers, often with loss of staining qualities. The baskets and dendrites of

the Purkinje cells were much better preserved. Fat was not demonstrated. Glial reaction was absent, except in comparatively rare instances of Purkinje-cell loss or damage, where proliferation of the Bergmann cells was observed; such damage, as a rule, was limited to single cerebellar folia or to parts of them.

The nuclei of the granule cells in the normal cerebellum either appear homogeneously blue in Nissl and hematoxylin-eosin stains, or show varying numbers of more or less well-defined, occasionally fused chromatin particles against a lighter background. In the process under discussion, they tended to conglutinate and to become deformed. Some nuclei shrank, stained poorly, and had irregular outlines with minute particles breaking away from their periphery. Some were diffusely hyperchromatic or had mulberry shape (Schrappe's[17] "morula status"). Others were slightly swollen and pale. Vacuolation and liquefaction (Schrappe's[17] "status bullosus") were observed in some nuclei. In terminal stages we saw a few scattered pale or dark minute fragments. However, we also found cases in which nuclear changes were relatively mild and the increase of eosinophilic interstitial material gradually appeared to supersede the nuclei. The number of the latter was decreased; they tended to form irregular clumps but to look rather normal, with occasional presence of small morular or light ones. Similar or identical involvement has been described in detail in other pathologic conditions by many authors (Leigh and Meyer,[18] Schrappe[17]).

Since there are closely associated anatomical and functional relations between olivary nuclei and granule cells, one might expect to see correspondingly severe olivary lesions. This, however, was not so. Mild degrees of outfall, fatty metamorphosis, and pyknosis were noted in certain cases. The significance of this finding should not be overrated. It has been known for many years that similar olivary changes accompanied by plasmatic gliosis occur often in routine autopsy material; this fact was rightly emphasized by Schrappe.[17]

The cerebellar lesions in our cases were often so impressive that we felt that they should have had clinical significance. General cerebellar deficit, especially the vermis syndrome, with difficulty in maintaining the erect position and in walking, may certainly occur in chronic and acute alcoholism. Unfortunately, the paucity of our clinical data did not permit definite statements. Moreover, in most cases the lesions appeared to be too fresh to have produced long-standing signs. However, it is of considerable interest that Skillicorn[19] recently has reviewed pertinent older observations of various authors and has described presenile cerebellar ataxia in chronic alcoholics aged between 39 and 55. While autopsy studies were not available in his patients, it may be surmised that a similar pathologic process was operative, perhaps of a relatively mild degree; the duration of the illness in Skillicorn's cases was from 1 to 15 years.

As far as the pathogenesis is concerned, we felt that we were dealing with a "selective parenchymal necrosis"; the granular layer apparently exhibits increased or selective vulnerability either to certain noxious agents or to the lack of certain vital substances. It was not feasible to explain the development of the alteration on the basis of circulatory disturbances. This conclusion has been reached not only by us but also by other authors who have studied the alteration in nonalcoholic patients. If anoxia or "hypoxidosis" were solely responsible, we should expect a focal pattern of the lesions, damage to Purkinje cells, and parenchymal changes in other locations.

The question of the specific etiology is difficult to answer. It would appear that a multiplicity of agents may produce the lesion, which in man is seen mainly in alcoholism, visceral cancer with gastrointestinal disturbances, hyper- and hypoglycemia (Leigh and Meyer[18] and others), and mercury bichloride poisoning (Hunter and

Russell [20]); and experimentally in various poisonings, especially with thiophene (thiofuran), (Upners [21]) and mercury bichloride (Noetzel [22]), and in radiation response (Hicks, Wright, and Leigh [23]; Alvord and Brace [24]). Routine microscopic examination of the cerebellum in unselected autopsy material may disclose additional conditions in which the lesion is present.* At this time we may say that toxins, metabolic disturbances, and nutritional deficiencies probably are responsible. The latter possibility was favored by Leigh and Meyer.[18]

More specifically, it is conceivable that disturbances in fat and ketone metabolism may be essential. In cases of malnutrition or of inadequate utilization of carbohydrates, ketones are formed in large amounts, predominantly from lipids in the liver. Ketonemia may cause acidosis with deleterious effects on the central nervous system. Chronic alcoholism appeared to be the essential prerequisite in our material; a preterminal severe acute intoxication may have done its share to bring about a rapid and profound disintegration of a vulnerable and previously damaged system.

Severe degrees of cerebellar degeneration, as seen in our material, apparently were incompatible with longer duration of life. Late stages were not observed by us. If patients were to survive for long periods, the probable pathologic picture would be that of atrophy, gliosis, and calcification and would resemble that described in other conditions by Ule,[25] Hunter and Russell,[20] and Noetzel.[22]

The susceptibility of the cerebellum to agents operative in conjunction with chronic alcoholism has again been established by our studies. Future investigation will have to get more facts concerning the varying degrees of participation of Purkinje cells and/or granular layer.

We must admit that we do not know why this "shift to the cerebellum" has taken place. Does the quality of the alcoholic beverages, and does coaction of barbiturates play a role? What is the significance of the terminal disease and of the liver damage? Does the reactivity of different brain regions change with the passing of time, prompted by factors yet unknown? The increase in the frequency of Marchiafava-Bignami disease would point in this direction.

This paper has dealt exclusively with problems of the neuropathologic aspects of alcoholism, in a perhaps one-sided material. It is highly desirable that an attempt at interconnecting clinical and anatomical findings be made again, using a large and well-chosen number of pertinent cases, for the clinical picture, too, must have changed over the last decades.

In conclusion, it would appear from our material that, to some extent at least, the old neuropathologic picture of chronic alcoholism, characterized by lesions in the interbrain, is fading away and is tending to be replaced by interesting but entirely nonspecific cerebellar alterations.

Summary

Histologic examination of the brains of 42 alcoholics showed that the formerly frequent lesions of Wernicke's disease have become very rare in recent years, and that a more or less severe but nonspecific degeneration of the cerebellar granular layer is a relatively common occurrence.

1050 Clermont St. (20).

REFERENCES

1. Courville, C. B.: Effects of Alcohol on the Nervous System of Man, Los Angeles, San Lucas Press, 1954.

2. Wernicke, C.: Lehrbuch der Gehirnkrankheiten, für Aerzte und Studirende, Kassel and Berlin, T. Fischer, 1881.

3. Gudden, H.: Klinische und anatomische Beiträge zur Kenntniss der multiplen Alkoholneuritis nebst Bemerkungen über die Regenerationsvorgänge im peripheren Nervensystem, Arch. Psychiat. 28:643-741, 1896.

4. Gamper, E.: Zur Frage der Polioencephalitis haemorrhagica der chronischen Alkoholiker: Anatomische Befunde beim alkoholischen Korsakow und ihre Beziehungen zum klinischen Bild, Deutsche Ztschr. Nervenh. 102:122-129, 1928.

* H. Jacob saw it in acute necrotizing enteritis (discussion remark quoted by Ule [25]).

5. Neubuerger, K. T.: Über die nichtalkoholische Wernickesche Krankheit, insbesondere über ihr Vorkommen beim Krebsleiden, Arch. path. Anat. 298:68-86, 1936.

6. Neubuerger, K. T.: Wernickesche Krankheit bei chronischer Gastritis: Ein Beitrag zu den Beziehungen zwischen Magen und Gehirn, Ztschr. ges. Neurol. 160:208-225, 1937.

7. Dammann, H. J.: Über Polioencephalitis haemorrhagica Wernicke bei Resorptionsstörung des Magen-Darmkanals, Arch. Psychiat. 188:72-80, 1952.

8. Rupp, C., and Riggs, H. E.: Case History, Clinical Pathological Conference, Neurology 3: 779-782, 1953.

9. Orlando, J. C.: Enfermedad de Marchiafava-Bignami: Sobre la degeneración sistemática de las comisuras cerebrales en el alcoholismo crónico, Neuro-psiquiat. 3:97-142, 1952.

10. Riese, W.; Jones, G. L.; Beamer-Maxwell, E., and Davis, H. E.: Marchiafava-Bignami Disease: Report of a 2d Case in Native-Born Americans, J. Neuropath. & Exper. Neurol. 13:501-504, 1954.

11. Seitelberger, F., and Berner, P.: Über die Marchiafavasche Krankheit, Arch. path. Anat. 326:257-277, 1955.

12. Neubuerger, K. T.: Über Hirnveränderungen bei Alkoholmissbrauch (unter Berücksichtigung einiger Fälle von Wernickescher Krankheit mit anderer Ätiologie), Ztschr. ges. Neurol. 135:159-209, 1931.

13. Stender, A., and Lüthy, F.: Über Spätatrophie der Kleinhirnrinde bei chronischem Alkoholismus, Deutsche Ztschr. Nervenh. 117-119: 604-622, 1931.

14. Santha, K.: Lokalisierte Atrophie der Kleinhirnrinde bei chronischem Alkoholismus, Monatsschr. Psychiat. 116:346-363, 1948.

15. Feyzulaeff, A. Z., and Sukhova, I. A.: Clinical and Pathohistological Study of Alcoholic Ataxia, Zhur. nevropat. i psikhiat. 55:501-595, 1955.

16. Meyer, A.: The Wernicke Syndrome, J. Neurol. Neurosurg. & Psychiat. 7:66-75, 1944.

17. Schrappe, O.: Frühschäden des Kleinhirns, Arch. Psychiat. 193:229-242, 1955.

18. Leigh, A. D., and Meyer, A.: Degeneration of the Granular Layer of the Cerebellum, J. Neurol. Neurosurg. & Psychiat. 12:287-296, 1949.

19. Skillicorn, S. A.: Presenile Cerebellar Ataxia in Chronic Alcoholics, Neurology 5:527-534, 1955.

20. Hunter, D., and Russell, D. S.: Focal Cerebral and Cerebellar Atrophy in a Human Subject Due to Organic Mercury Compounds, J. Neurol. Neurosurg. & Psychiat. 17:235-241, 1954.

21. Upners, T.: Experimentelle Untersuchungen über die lokale Einwirkung des Thiophens im Zentralnervensystem, Ztschr. ges. Neurol. 166:623-645, 1939.

22. Noetzel, H.: Schädigung und Verkalkung der Körnerschicht des Kleinhirns bei chronischer experimenteller Sublimatvergiftung, Beitr. path. Anat. 115:226-236, 1955.

23. Hicks, S. P.; Wright, K. A., and Leigh, K. E.: Time-Intensity Factors in Radiation Response, A. M. A. Arch. Path. 61:226-238, 1956.

24. Alvord, E. C., and Brace, K. C.: X-Ray Induced Pyknosis of Cerebellar Granule Cells in Guinea-Pigs and Its Suppression by Barbiturate Anesthesia, Second International Congress of Neuropathology, London, England, 1955, to be published.

25. Ule, G.: Kleinhirnrindenatrophie vom Körnertyp, Deutsche Ztschr. Nervenh. 168:195-226, 1952.

Disseminated Nodular Pulmonary Ossification with Mitral Stenosis

HUGO E. DAUGAVIETIS, M.D., and LORENZ S. MAUTNER, M.D., Toronto, Canada

Bone formation in the lung in a young woman with dropsy was first described by Wagner in 1859,[3] but only in 1932 did Salinger for the first time correlate disseminated parenchymatous pulmonary ossifications with mitral stenosis.[1]

Several reports have appeared in the literature since, but the total number of cases described is still comparatively small, all authors emphasizing the rarity of this condition. No statistical surveys have been found in the literature of recent years, but in 1949 Lawson,[4] in England, was able to collect only 40 cases. In the same year Pendergrass and co-workers [5] found no autopsy reports in the American literature and only 17 cases recorded in the world literature, but not all of these showed a typical x-ray pattern.

In view of this, it was felt that the case observed by us merits publication. No attempt is being made to offer a theory of pathogenesis on the basis of this one observation.

Report of a Case

A 30-year-old man was first seen in the medical outpatient department of this hospital, in April, 1954, because of dull and steady epigastric pain which increased on exertion, and decreased exercise tolerance of six months' duration. There was a past history of rheumatic fever at the age of 11 years. Physical and laboratory findings, EKG, chest x-ray, and fluoroscopic findings confirmed the diagnosis of chronic rheumatic heart disease in failure with mitral stenosis and regurgitation; auricular fibrillation followed about a month later. Remarkable was the appearance of the lungs in x-ray film, showing multiple small dense opacities, measuring up to 8 mm. in diameter, throughout both lung fields, more marked in the hilar areas, bases, and apices. The radiological diagnosis of hemosiderosis associated with mitral stenosis was made.

He was admitted to hospital on several occasions during the following one year and nine months and was followed in the cardiology clinic in the intervals between the hospital admissions. During his first two hospital admissions, on two occasions, an attempt was made to convert the auricular fibrillation to sinus rhythm by means of quinidine, but each time he developed clinical jaundice after about five days on this medication. The jaundice subsided in a few weeks after discontinuation of medication. With appropriate treatment his heart failure improved, but temporarily only. Although the case did not appear to be an ideal one for mitral commissurotomy, because of the associated mitral regurgitation, the prognosis on conservative management being considered poor, it was decided to explore the mitral valve with the hope that correction of the stenosis might prolong his life.

The operation was performed on Nov. 10, 1954. Both cusps of the mitral valve were found to be markedly calcified, and there was evidence of severe mitral stenosis and quite marked mitral regurgitation. A very slight attempt was made to increase the size of the opening, but, as it appeared that the regurgitation was going to be made worse by this, no further procedure was carried out. A biopsy specimen of the lingula of the left lung was taken; unfortunately, the ossified nodule which was found on gross examination of the specimen was lost while preparing the microscopical section. The left auricular appendage showed no Aschoff nodules microscopically.

After the operation an acute episode of rheumatic fever developed, which subsided on cortisone treatment. The patient did not benefit from this operative procedure, but did not require further hospitalization for one year. At the time of his final admission, on Nov. 3, 1955, he was cyanosed, in moderate respiratory distress, and was coughing up blood-tinged sputum. There was evidence of jugular venous distention and slight ankle edema. The heart was markedly enlarged clinically, as well as radiologically; auricular fibrillation was present, the rate being 84 a minute. There were apical systolic thrill, accentuation of the first mitral

Submitted for publication July 21, 1956.

Department of Pathology, St. Joseph's Hospital.

Fig. 1.—Chest x-ray.

sound, and systolic and diastolic mitral murmurs. B. P. 120/85. Bilateral basal rales were present. There was marked distention of the abdomen, with shifting dullness, and the liver was enlarged 4 fingerbreadths below the right costal margin. X-ray of the chest revealed the previously described multiple dense opacities in the lung fields, which had not changed in appearance to any extent as compared with the first film, taken one and one-half years previously.

The patient's course was a fairly rapidly downhill one, and he died on Jan. 6, 1956.

Autopsy

Autopsy was performed six hours after death. The body was that of a moderately well-nourished and moderately jaundiced man, showing pressure sores over the sacral area and edema of the external genitalia and lower limbs.

The right pleural cavity contained 1000 cc., the left 600 cc., of clear, straw-colored fluid, and there were pleural adhesions on the left side along the incision scar. The right lung weighed 730 gm., and the left lung weighed 650 gm. Both lungs were grayish-brown to dark-brown in color and showed numerous coarsely granular, yellowish-white nodules of bony consistency, measuring 2 to 8 mm. in diameter, which were scattered throughout both lung fields, apparently without any particular distribution. Moderate amounts of blood and hemorrhagic, frothy fluid escaped on the cut surface, and similar frothy material was found in the trachea and the bronchial tree, the mucosa of which was somewhat congested. Pulmonary vessels were not remarkable.

There was evidence of extensive adhesive pericarditis, but the adhesions could be separated by blunt dissection. The heart weighed 720 gm. and showed gross hypertrophy and dilatation. The right ventricle measured 1.1 and the left 1.5 cm. in thickness. The mitral valve was markedly stenosed, the opening measuring 0.4×0.2 cm. in diameter only. There were marked thickening and calcification of the valve cusps, which showed complete fusion, so that the commissures could not be recognized. Calcified vegetations were seen on the atrial surface of the valve.

The peritoneal cavity contained 1000 cc. of clear, straw-colored fluid. The liver weighed 1615 gm. and was moderately firm in consistency, the surface being discolored a yellowish brown, with scattered irregular, deeper-yellow areas. On the cut surface marked dilatation of the veins and evidence of marked congestion could be seen. Small, irregular, comparatively deep-yellow areas were seen scattered irregularly throughout the cut surface. The rest of the abdominal viscera showed marked passive congestion only.

Fig. 2.—Postmortem x-ray, right lung.

Microscopical Examination

The lungs revealed marked congestion, patchy increase in interstitial connective tissue, particularly in the perivascular position, and numerous hemosiderin-containing macrophages in air spaces, bronchial lumina, and interstitial tissue. In some areas the macrophages were arranged in small nodules, the intervening lung tissue showing practical absence of pigment macrophages. Several small tributaries of pulmonary vein showed thrombi, and in one area a small branch of a pulmonary artery showed marked medial thickening; otherwise, no vascular changes were observed. The air spaces showed fetalization in many areas surrounding the hemosiderotic nodules. Numerous bony nodules were found in the air spaces; they varied in size, occupying one or several adjacent alveoli, and were round or mulberry-shaped. They showed lamellar structure, with osteocytes and small vascular channels in the bone tissue, but no bone marrow was seen. In the periphery of some of these bony nodules osteoid tissue was found, and some osteoblasts in these areas could be seen. The wall of the air spaces was not adherent to the bony structures but extended into some of the crevices. The Weigert-Van Gieson elastic tissue stain showed absence of elastic tissue in the bony nodules. Perls' iron stain in several sections examined showed slight bluish discoloration of the periphery of the bony nodules in some areas. However, additional rinsing with water caused complete decolorization of these areas. Therefore, it was felt that the positive iron stain most likely did not depend on the iron content of the bony structures but probably was due to contamination by surrounding iron-containing soft tissue, produced by the microtome knife in preparing the section.

A section from the heart showed marked thickening of pericardium with hyperemia, hemorrhages, edema, fibrin deposits on the surface, and mononuclear-cell collections. Myocardial fibers appeared to be hypertrophic. In some areas slight endocardial scarring with infiltration by mononuclear cells was found. Section from the mitral valve showed marked thickening of the valve with vascularization. Large calcified areas could be found at the base of the valve with deposits of eosinophilic-staining material resembling osteoid tissue between the clumps of calcium. No osteocytes were seen. Scarred and calcified vegetations were found on the auricular surface of the mitral valve near its base. No evidence of Aschoff nodules was found in the numerous sections examined.

Sections from the liver showed complete disruption of normal liver architecture, the periportal areas being better preserved, with some increase in the fibrous tissue. In other areas liver lobules were completely necrotic and replaced by fibrous tissue, showing proliferating bile ducts. No central veins were seen. There were also areas of hemorrhage and fatty metamorphosis. No definite evidence of regenerating liver tissue was found.

Otherwise, the microscopical findings were not remarkable apart from evidence of congestion in the abdominal viscera.

Comment

Most authors have stressed the association of disseminated pulmonary ossification with hemosiderosis, but there is a considerable difference of opinion whether bone formation represents the end-result of organization of hemosiderin deposits, through successive stages of fibrosis, calcification, and ossification, or whether the relation between pulmonary ossification and hemosiderosis is a coincidental one.[16,17]

A history of rheumatic fever followed by mitral stenosis is present invariably, although there are a few reports of pulmonary hemosiderosis in chronic left ventricular failure in nephrosclerosis and in any form of pulmonary hemorrhage repeated over a long period of time.[4,18] No cases have been observed in association with rheumatic aortic valve lesions.

The condition occurs mostly in young people, the average age in one series being

35 years. The oldest reported case was 58 years of age.[1,5,9]

Remarkable is the predominance of males. In one series the ratio of males to females was given as 4:1, which is surprising considering the more frequent occurrence of mitral stenosis in females.[9]

The pathogenesis is not clear, there being several theories, none of which is completely satisfactory and explains the age and sex distribution or the absence of similar lesions in rheumatic aortic valve disease.

Most authors feel that chronic passive pulmonary congestion associated with pulmonary hypertension, small repeated hemorrhages, and hemosiderin deposits in clumps or macrophages is the important preceding pathological condition, the chronic venous stasis promoting bone formation. The reasons for the nodular distribution of the macrophages are not known.[3-7,10,12,16]

A second group of authors propose a previous interstitial rheumatic pneumonia as the preceding lesion, with organization of intra-alveolar exudate, which has probably a specific quality of producing ossification.[1,3,8]

Still others emphasize the possible importance of both factors, namely, chronic interstitial pneumonia and chronic pulmonary congestion.[15]

Another theory tries to explain the bone formation as the result of ossification of the fibrinous exudate of a localized area of pulmonary edema, there being no certainty about factors producing this exudate.[17]

Lastly, thrombosed septal capillaries are thought to be the origin of the ossification. They may protrude into the alveoli or become completely detached from the alveolar walls, and mesenchymal cells from the septa, which are attached to the capillary surface, are thought to be concerned with the formation of bone.[14]

Clinical studies have given similarly disappointing results. Although the majority of cases show evidence of pulmonary hypertension and congestion, there are also re-

Fig. 3.—Lower lobe of right lung. Multiple intra-alveolar areas of ossification and presence of siderophages within one alveolus. Hematoxylin-eosin stain; reduced to 8/9 of mag. × 40.

Fig. 4.—Area of ossification with peripheral deposition of osteoid. Hematoxylin-eosin stain; reduced to 8/9 of mag. × 120.

ports of cases with similar lesions without any clinical or radiological evidence of pulmonary congestion.[1,4] There is no parallelism between the remarkable alterations in the x-ray picture and hemodynamic disorders.[16] Several authors stress the occurrence of pulmonary ossification in long-standing mitral stenosis and prolonged mild congestion[9,12]; others feel that there is no correlation between the radiological findings and duration of the heart disease or severity of the heart failure.[3] Biochemical studies, particularly regarding Ca and P changes in the blood, have given normal results.[16]

The x-ray picture varies from very fine stippling to generalized fine nodulation of the lung, the nodules varying in size from pinhead- to pea-sized, in shape from round and discrete to mulberry, and in density, this being dependent upon the presence and degree of hemosiderosis, on one hand, and of ossification, on the other.

The densities are found commonest in the bases and central parts of the lungs and decreasing toward the periphery, but they may also occur in the upper lung fields, and even the apices. Usually there is an associated hilar vascular engorgement. The differential diagnosis includes more than 20 various conditions causing miliary nodulation of the lungs.[1,3,5,12]

Gross examination of the lungs usually shows evidence of brown induration and innumerable bony nodules scattered throughout the lung fields, most marked in the lower lobes, varying from pinhead- to small-pea-sized and being grayish white in color. Calcified plaques may be present in large numbers or practically absent on the visceral pleura. In some cases atheroma of the pulmonary artery has been observed.[1,4,7,17]

The microscopical findings vary considerably. A constant finding appears to be chronic passive congestion with occasional thrombi in the capillaries and smaller branches of pulmonary artery. Patchy interstitial fibrosis and occasional degenerative changes in the interstitial tissue with infiltration by mononuclear cells have been observed frequently, but there is no evidence of fibrosis in the area surrounding the ossified nodule.

Groups of alveoli are packed by heart failure cells, the intervening lung tissue showing only a few macrophages in the alveoli. Many alveoli are seen lined by cuboidal epithelium.

The bony nodules fill one alveolus, or a group of alveoli with their alveolar duct, and appear to be lying free in the air spaces. These nodules are of the woven type, rounded or with irregularly crenated outline, having a concentric lamellar appearance, and containing blood vessels but no bone marrow. Some nodules show a central ossified zone with peripheral addition of osteoid tissue with osteoblasts. Also, acellular intra-alveolar material resembling osseous ground substance has been described, but no calcification has been seen by most authors. The bone does not take up an iron stain, but elastic fibers have been demonstrated in the nodules in some cases.

Most controversial, however, are the described vascular changes. While most authors deny any vascular changes in the interstitial tissue, Elkeles and Glynn, and Vincent and Sokal have described severe degenerative and inflammatory changes in the smaller pulmonary vessels and vascular proliferation around the bony nodules.[1,4-7, 12,14-17]

The case under discussion presents typical x-ray, gross, and microscopic findings of disseminated nodular pulmonary ossification associated with mitral stenosis. We were unable to demonstrate any degenerative, inflammatory, or proliferative vascular changes on microscopical examination. Even so, no elastic fibers, as described by Elkeles and Glynn, were found in the bony nodules.

The etiology of the extensive necrotic changes and replacement fibrosis of the liver could not be established with certainty, but it was felt that a combination of chronic passive congestion and additional toxic

damage to the liver by quinidine was the most likely cause.

No information regarding the duration of the pulmonary ossifications could be obtained, the patient showing marked radiological changes in the lungs when seen first in the medical outpatient department, at which time he had had symptoms related to cardiac failure for six months only. No further progression of the pulmonary lesions could be observed during the following 21 months of follow-up. Biochemical studies regarding calcium and phosphorus metabolism and pH of the blood were not carried out during his hospitalization.

Summary

1. A case of disseminated nodular pulmonary ossification in association with mitral stenosis in a 30-year-old man is described.

2. The literature is reviewed, stressing the uncommon occurrence of this condition, the age and sex distribution, the various theories of pathogenesis, and the radiological and pathological findings.

St. Joseph's Hospital, Sunnyside.

REFERENCES

1. Elkeles, A., and Glynn, L. E.: Disseminated Parenchymatous Ossification in the Lungs in Association with Mitral Stenosis, J. Path. & Bact. 58:517, 1946.

2. Scott, L. D. W.; Park, S. D. S., and Lendrum, A.: Symposium: Clinical, Radiological and Pathological Aspects of Pulmonary Haemosiderosis, Brit. J. Radiol. 20:100, 1947.

3. Elkeles, A.: Disseminated Ossified Nodules in the Lungs Associated with Mitral Stenosis, Proc. Roy. Soc. Med. 40:405, 1947.

4. Lawson, H. M.: Disseminated Ossifications of the Lungs in Association with Mitral Stenosis, Brit. M. J. 1:433, 1949.

5. Pendergrass, E. P.; Lame, E. L., and Ostrum, H. W.: Hemosiderosis of the Lung Due to Mitral Stenosis, Am. J. Roentgenol. 61:443, 1949.

6. Sahn, S. H., and Levine, I.: Pulmonary Nodules Associated with Mitral Stenosis, Arch. Int. Med. 85:483, 1950.

7. Wier, J. A.; Piccoli, A. J.; Greene, D. G., and Greene, C. W.: Mitral Stenosis with Exertional Cyanosis and Pulmonary Hemosiderosis, Circulation 6:868, 1952.

8. Vincent, J., and Sokal, G.: Ossification pulmonaire nodulaire dans un cas de sténose mitrale, Rev. belge. path. méd. expér. 23:111, 1953.

9. Haubrich, R., and Versen, E.: Über die miliare Lungenhämosiderose im Röntgenbild, Fortschr. geb. Röntgenstrahlen 81:346, 1954.

10. Taylor, H. E., and Strong, G. F.: Pulmonary Hemosiderosis in Mitral Stenosis, Ann. Int. Med. 42:26, 1955.

11. The Lungs in Mitral Stenosis, Leading Article, Lancet 2:708, 1955.

12. Haubrich, R.: Miliary Haemosiderosis of Lungs with Partial Ossification, in The Year Book of Radiology (1955-1956 Year Book Series), edited by J. F. Holt, F. J. Hodges, H. W. Jacox, and M. M. Kligerman, Chicago, The Year Book Publishers, Inc., 1955.

13. Hamer, N. A. J.: Idiopathic Pulmonary Haemosiderosis in a Young Adult, Brit. M. J. 1:1008, 1955.

14. Terplan, K. L.: Pathogenesis of Tuberous Bone Formation in the Lung, Am. J. Path. 22: 632, 1946.

15. Wells, H. G., and Dunlap, C. E.: Disseminated Ossification of the Lungs, Arch. Path. 35: 420, 1943.

16. Pezzuoli, G.; Gasparini, V., and Folli, G.: Ossifications pulmonaires disséminées dans le rétrécissement mitral, Presse méd. 63:972, 1955.

17. Whitaker, W.; Black, A., and Warrack, A. J. N.: Pulmonary Ossification in Patients with Mitral Stenosis, J. Fac. Radiologists 7:29, 1955.

Death Due to Bone-Marrow and Tumor Embolization in the Absence of Fracture

Report of a Case

FRANK H. DeLAND, M.D., and WARREN A. BENNETT, M.D., Rochester, Minn.

Lengemann [1] observed the phenomenon of bone-marrow embolism to the lung 70 years ago. Since that time only 57 such cases have been reported in the literature. In most of these cases the condition occurred as a result of fracture. However, marrow embolization in the absence of fracture has been reported by several authors.[2-4] One of Lengemann's [1] original observations was made in two women who died of eclampsia. Rappaport and associates [2] reported finding bone-marrow embolism in the absence of fracture subsequent to such convulsive states as tetanus, shock therapy, eclampsia, and drug allergy. Polayes [4] also reported an instance of the condition in an eclamptic woman. Lengemann,[1] Lubarsch,[3] and Rappaport [2] wrote that marrow embolization could occur in the absence of fracture. Ogata [5] proved this phenomenon experimentally. He subjected rabbits to bony "concussion" and demonstrated pulmonary-marrow emboli without osseous fracture.

Pulmonary fat embolism from the marrow of bone as a primary cause of death has been reported many times. Yet there is only one case in the literature [6] in which the reporter felt that bone-marrow embolization by itself was the cause of death. The patient had had extensive tuberculous spondylitis. Manipulation of the legs during positioning for cystoscopy was believed to have caused compression fractures of several vertebrae, although the fractures were not observed at necropsy. Previously we studied 70 cases of bone-marrow embolism,[7] and in none of them was the embolization massive enough to be considered the primary cause of death. In the case we shall present death resulted from massive embolization from both bone marrow and metastatic tumor of the vertebrae in the absence of fracture. No comparable case has been noted in the literature.

Submitted for publication July 27, 1956.

Fellow in Pathology, Mayo Foundation (Dr. DeLand). Section of Pathologic Anatomy, Mayo Clinic and Mayo Foundation (Dr. Bennett). The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Report of Case

Clinical Aspects.—A 71-year-old white man was admitted complaining chiefly of pain in the left lower leg, low backache, and an enlarging nodule of the skull. The patient had been in good health until four months prior to his admission, when a sore throat developed, followed by lumbosacral backache. The backache persisted in spite of treatment, and two weeks prior to his admission pains developed in the left lower leg. He had lost 12 lb. during the previous 4 months. An enlarging nodule on the vertex of the skull had been present for a month. He had had nocturia two to three times.

The patient was chronically ill. A soft, fluctuant nodule was found over the vertex of the skull. The lungs were clear. There was a questionable mass in the right lower abdominal quadrant, extending to the pubis at the midline. Prostatic examination disclosed a non-nodular moderate enlargement and marked fixation of the prostate gland to the surrounding tissue. There were no palpable lymph nodes. Results of urinalysis were within normal limits. Erythrocytes numbered 3,043,000; leukocytes, 6,500 per cubic millimeter of blood. The value for urea was 32 mg. per 100 cc. of blood; acid phosphatase, 16.9 King and Armstrong units per 100 cc. of serum; alkaline phosphatase, 43 King and Armstrong units per 100 cc. of serum, and the albumin-globulin ratio was 4.6/2.4. A roentgenogram of the thorax disclosed fibrosis in the field of the middle part of the left

lung. A roentgenogram of the skull demonstrated an irregular area, about 3 mm. in diameter, of rarefaction in the vertex of the skull near the coronal suture, consistent with the appearance of a metastatic malignant process. A roentgenogram of the kidney, ureter, and bladder revealed osteoporosis of the spinal column, with old compression of several lumbar vertebrae. Residual urine amounted to 175 cc.

Transurethral resection with bilateral orchidectomy was advised and accepted. Twenty-six grams of tissue was removed. The surgical pathologic report of the prostate tissue was Grade 2 adenocarcinoma, with areas of a higher malignancy.

Approximately 15 hours later shock developed. The pulse was 140 a minute, and was faint and rapid; blood pressure was 70 mm. of mercury systolic; diastolic pressure could not be obtained. The skin was cold and clammy. The patient was given a pint of compatible whole blood within two hours. At the end of that time his condition was markedly improved; blood pressure was 100 diastolic and 80 systolic; the pulse was 100 per minute; the skin was warm and dry. Administration of a second unit of blood was started at that time and was completed within another two hours. The condition of the patient appeared to be satisfactory, except for some restlessness and mental confusion. Emergency determinations of urea and hemoglobin were 66 and 11.7 mg., respectively, per 100 cc. of blood. His condition continued to be good until the next morning, two days postoperatively. On that morning the patient was being assisted from his bed into a chair when he suddenly died.

Postmortem Examination.—Thick, frothy, yellowish mucus was present in the trachea. The peritracheal lymph nodes were enlarged. The right lung weighed 475 gm. and the left lung 460 gm. The external surface of the lungs appeared to be normal. Sectioning did not disclose pulmonary emboli or infarcts grossly. There was essentially no pulmonary edema. The periaortic and superior mesenteric lymph nodes were enlarged and firm. A small polyp of the rectum was located 4 cm. above the anorectal junction; it was 3 by 3 by 5 mm. on a 5 mm. pedicle. There was moderate trabeculation of the bladder. The lining of the prostate gland was shaggy and was coated with clotted blood. The body of the ninth thoracic vertebra contained a metastatic nodule 1 cm. in diameter. Just anterior and to the left of the bregma, beneath the scalp, was a soft hemorrhagic mass, 4 by 2.5 cm., involving the outer cortex and the medullary portion of the cranium down to the inner table. No fractures were found.

Histologic Examination.—There was a Grade 2 adenocarcinoma of the prostate gland, with perineural involvement and metastatic processes in the periaortic lymph nodes, the vertebral marrow, and the skull. All lobes of the lung showed the same pathologic process, namely, massive embolization of the pulmonary vasculature with Grade 2 adenocarcinoma (identical with that of the prostate gland and bone marrow). Fat stains showed moderate fat embolization of all lobes. No infarcts were present, and edema was minimal. In the rectal polyp there was a Grade 1 adenocarcinoma limited to the mucosa.

Comment

This case is an example of sudden death due to massive pulmonary embolization resulting from medullary fracture without cortical fracture. In view of the patient's age, the source of the bone marrow would have to be essentially one of four: the skull, the ribs, the sternum, or the vertebrae. There was no history of trauma at any time to indicate actual fracture in any of these locations. Therefore, it is reasonable to assume that bony "concussion" of the vertebrae, caused by the strain of cystoscopy or moving from the bed, or both, resulted in "medullary fracture" and release of marrow emboli. The marrow emboli in the pulmonary vasculature were very typical, containing all the elements and the structure of bone marrow (Fig. 1*a*) and were in no way different from the picture in a section of bone marrow taken from one of the vertebrae. Ten microscopic sections of the lung, distributed equally throughout all the lobes, were examined. Nearly all the pulmonary arteries contained emboli, either of bone marrow or of tumor tissue that could be identified as adenocarcinoma (Fig. 1*b*). All the tumor emboli were bland; that is, no evidence was seen to indicate that the tumor was organized or growing within the parenchyma of the lungs. The tumor emboli were very similar histologically to the areas of adenocarcinoma in the vertebra (Fig. 2*a*), which, in turn, were identical with the tumor in the prostate gland (Fig. 2*b*). In one of the sections of tissue from the lungs (Fig.

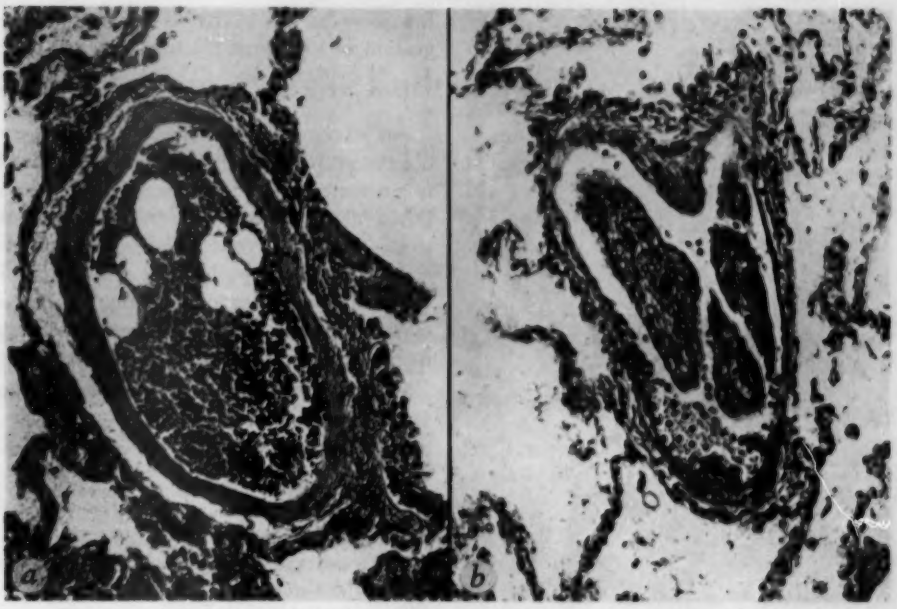


Fig. 1.—(*a*) Section of tissue from the lung, showing bone-marrow embolism in a pulmonary artery (hematoxylin and eosin; reduced about 4% of mag. × 150). (*b*) Section of tissue from the lung, showing tumor embolus in a pulmonary artery (hematoxylin and eosin; reduced about 4% of mag. × 200).

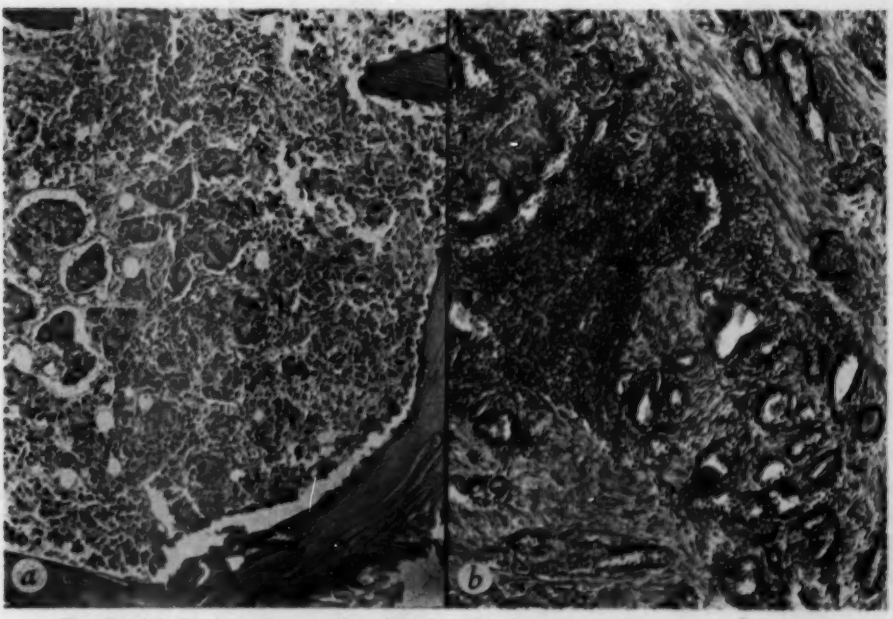


Fig. 2.—(*a*) Section of a vertebra (hematoxylin and eosin; reduced 4% of mag. × 100). (*b*) Section of tissue from the prostate gland, showing adenocarcinoma (hematoxylin and eosin; reduced 4% of mag. × 100).

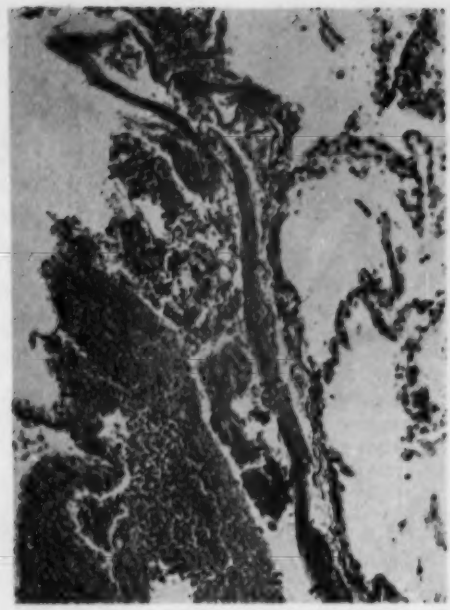


Fig. 3.—Section of tissue from the lung. An embolus composed of bone marrow (upper part) and tumor (lower part) lies between a blood clot and the wall of the vessel (hematoxylin and eosin; × 150).

3) there was an embolus containing both bone marrow and tumor tissue. It is not unreasonable to assume that the source of the marrow and tumor embolization was the vertebrae, and not any of the other possible sites. The vertebrae from the lumbosacral junction through the second thoracic vertebra were halved by handsaw, and no suggestion of vertebral fracture was noted.

Conclusion

An example of massive pulmonary embolization followed by instantaneous death is presented. The embolization was composed of bone marrow and metastatic tumor to the bone marrow. The source of the embolization was probably the vertebrae. It is concluded that strain precipitated medullary fracture of bone in marrow previously weakened by carcinomatous metastasis.

Section of Pathologic Anatomy, Mayo Clinic.

REFERENCES

1. Lengemann, P., cited by Lubarsch.[3]

2. Rappaport, H.; Raum, M., and Horrell, J. B.: Bone Marrow Embolism, Am. J. Path. 27: 407-434 (May-June) 1951.

3. Lubarsch, O.: Über Knochenmarkgewebs-Embolie, Arch. path. Anat. 151:546-549 (March) 1898.

4. Polayes, S. H.: Lung: Osseous Emboli After Spinal Tap in a Case of Waterhouse-Friderichsen Syndrome Complicating Preeclamptic Toxemia, Brooklyn Hosp. J. 11:38-39, 1953.

5. Ogata, S.: Megakaryocytanembolie und Knochenmarks-Embolie in Lungenkapillaren, Beitr. path. Anat. 53:120-128, 1912.

6. Gleason, D. F., and Aufderheide, A. C.: Fatal Bone Marrow Embolism Occluding the Pulmonary Arteries, Am. J. Med. 15:137-140 (July) 1953.

7. DeLand, F. H., and Bennett, W. A.: Bone Marrow Emboli in Trauma, unpublished data.

Carcinosarcoma of the Endometrium

An Unusual Case Receiving Estrogen Therapy for Eleven Years

CHARLES M. KARPAS, M.D., and FRANCIS D. SPEER, M.D., New York

This paper reports a case of carcinosarcoma of the endometrium, a true endometrial carcinosarcoma, developing in a patient given a prolonged course of estrogen therapy for 11 years. It also reviews briefly the pertinent literature concerning this somewhat confused subject. A feature of added importance is the fact that this complex endometrial neoplasm developed in a woman who had had bilateral oophorectomy a short time before the prolonged estrogen therapy was instituted. It has recently been shown that bilateral oophorectomy does not prevent endometrial carcinoma and that the ovaries need play no part in its development. These facts have been used to imply that estrogens, no matter what their source, are unrelated to endometrial neoplasia.

The term carcinosarcoma has been applied to those tumors consisting of both carcinomatous and sarcomatous elements arising within the same organ. Within the last 50 years, the literature is replete with numerous articles describing such neoplasms, employing variable and confusing terminology. At the present, these tumors are categorized as mixed, double, composition, collision, and mixed mesodermal, as well as *carcinosarcomatode, sarcocarcinomatodes,* sarcoma botryoides, and teratoma.

Virchow,[1] who labeled these tumors as carcinosarcomas, believed stromal or epithelial portions were sequentially or simultaneously stimulated to malignant growth. The possibility that carcinomatous and sarcomatous elements could arise from the same undifferentiated embryonic cells was noted by Läwen.[2] Though Borst [3] insisted that only true carcinosarcomas are those that arise simultaneously, Herzheimer [4,5] pointed out that a carcinoma could stimulate stromal growth to an excess, and that the latter upon proceeding to a stage of malignancy would be a carcinosarcoma. He also added that the secondary growth may supersede the primary. Krompecher [6] doubted the dual nature of the lesions and stated that they were derived from an embryonal cell which supposedly has the potentialities of both stroma and parenchyma. Meyer,[7] realizing that there was a definite lack of uniformity in the nomenclature, tried to achieve some sort of agreement by employing the following expressions: (1) collision tumors, two primarily independent tumors mutually invading each other; (2) combination tumor, the resultant malignant transformation of two different blastomatous portions arising from one stem cell, e. g., Wilms' tumor; (3) composition tumor, in which parenchyma and stroma become embryonal.

Ewing [8] declared, on the other hand, that many of these tumors did not contain carcinomatous and sarcomatous elements but, rather, showed the transformation of epithelial cells into transitional cells, simulating a sarcoma. Continuing with this concept, Saphir and Vass [9] reviewed 153 cases of so-called carcinosarcomas, including 8 cases reported by Frankl,[10] 36 of which were tumors of the uterus. The authors analyzed these cases in the light of the following complicating factors which could alter the microscopic appearance: (*a*) growth of a carcinoma into benign tumor, (*b*) inclusion

Submitted for publication July 21, 1956.

From the Laboratory of Surgical Pathology, New York Medical College, Flower and Fifth Avenue Hospitals.

of benign epithelial-cell formations within a malignant tumor of connective tissue origin; (*c*) chronic productive inflammation in the vicinity of the tumor; (*d*) marked anaplasia; (*e*) morphological variations in tumor cells (spindle forms of epithelial tumors); (*f*) history and histologic evidence of x-ray irradiation.

Goodfriend and Lapan [11] reported on 64 cases, of which they considered only 42 as authentic, with 22 doubtful ones. Dixon and Dockerty [12] accepted only 20 previous cases as authentic. Additional reviews and case reports have filled the literature.[13-19]

It is obvious that as more careful and critical gross and microscopic examinations are made, a smaller number of carcinosarcomas will be diagnosed. Of the vast number of gynecological specimens seen yearly at various institutions, malignant neoplasms of the endometrium account for a very small per cent. MacFarlane [20] gathered over a 20-year period 42,439 gynecological specimens at Montreal General and Royal Victoria Montreal Maternity Hospitals. Within this group, 0.94% were adenocarcinomas of the endometrium, while sarcomas were encountered at a frequency of 0.09%. Thus, the combination of two elements is truly a rarity. The incidence of a carcinosarcoma in corporal neoplasms is usually stated as 1%.[21] We feel this figure should be considered as the extreme upper limit.

Report of a Case

Clinical History.

A 43-year-old white woman entered Flower and Fifth Avenue Hospitals on Dec. 17, 1953, with a chief complaint of vaginal spotting. Her clinical chart recorded primagravida, Para O, abortus 1. Eleven years prior to admission, the patient was stated to have had an ectopic pregnancy, for which she underwent an exploratory laparotomy. A bilateral salpingo-oophorectomy was performed on finding only chronic pelvic inflammation. Following the surgery, patient was maintained on hormone therapy (conjugated estrogens [Premarin]), 1 tablet daily for seven years, and then 1 tablet a day for five days each month. During this 11-year period, the patient did have isolated periods of endometrial bleeding. Her record, however, reports no enlargement or symptoms referable to the breasts, and no loss of weight, hirsutism, or change of voice. The presence of moderate obesity is reported at the time of her second hospital admission, although her actual weight is not stated.

Six weeks prior to the present admission she noted a watery discharge, and beginning one week later, and persisting until the time of admission, there was intermittent spotting, occurring in three- to four-day periods. General physical findings were not remarkable. Pelvic examination revealed a slightly enlarged uterus, firm and freely movable; no tumors or masses were palpated in the adnexa. On Dec. 18, a uterine curettage was performed, which yielded a large amount of soft, edematous, and friable tissue. It was reported as a carcinosarcoma, showing adenocarcinoma, of endometrial origin, and sarcoma, most probably of stromal origin. The patient was reluctant to have the advised major surgery and was discharged. She was readmitted a month later, and a modified radical hysterectomy and iliac-node dissection was performed. The hospital course was prolonged as a result of a chemical burn to the buttocks, but otherwise she did well. She was discharged Feb. 16, 1953.

This woman has been followed as an outpatient and was last seen June 5, 1956, with no evidence of recurrence.

Surgical Specimen.

The uterus measured 12×5×5 cm. Section revealed 6×3×2 cm. polypoid mass, projecting into the endometrial cavity from the posterior wall. This mass showed a gray-white surface with soft, friable foci, and smooth, glistening regions. The edges, though overhanging, appeared to be quite distinct from the adjacent endometrium.

Microscopic Findings. The cellular pattern was quite varied. On the surface, and penetrating into the deeper areas, there were masses of epithelial cells, many of which formed atypical glands. The latter were lined by columnar cells, exhibiting loss of nuclear polarity, hyperchromatism, and atypical mitoses (Fig. 1). There were numerous papillary infoldings in the glands. Many of the epithelial elements were arranged in masses and irregular cords without structural orientation. Between these carcinomatous elements, and contrasting sharply with them, were clusters of spindle-shaped cells forming interlacing bundles (Fig. 2). Reticular fibers extended from these cells, which with Wilder's stain appeared to surround the individual nuclei.

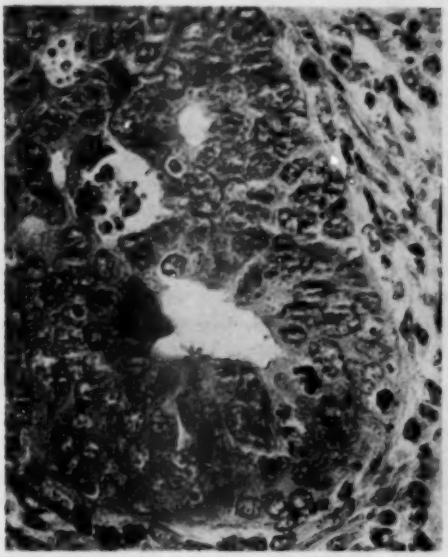


Fig. 1.—Adenocarcinomatous elements of the endometrial tumor. High-power view.

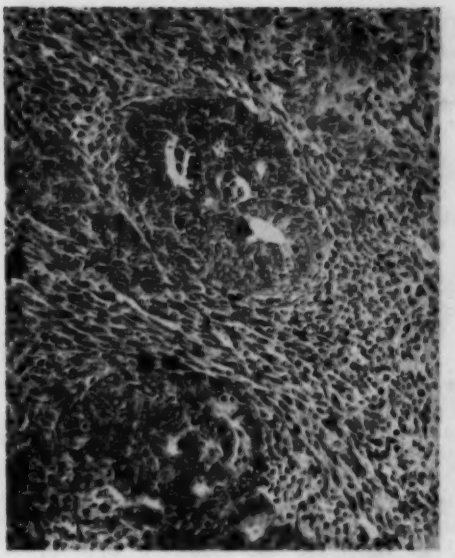
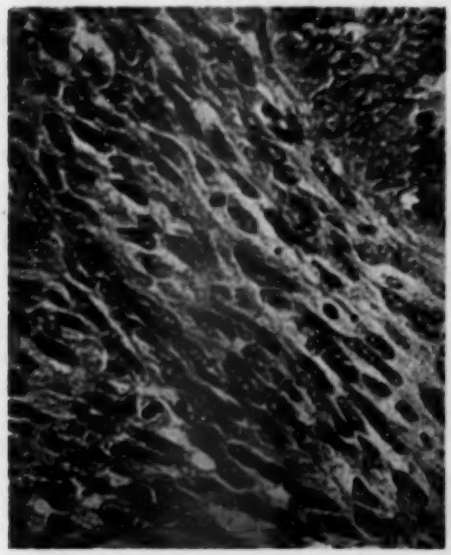


Fig. 2.—Both carcinomatous and sarcomatous elements of the endometrial tumor. Low-power view.

Employing Mallory's phosphotungstic acid-hematoxylin (PTA) stain, myofibrils could not be identified. Numerous mitotic figures were seen in all high-power fields. These stromal elements, with the aid of histochemical stains, appear to be characteristic of malignant fibroblasts (Fig. 3). Sections of the iliac nodes failed to demonstrate either carcinomatous or sarcomatous metastases.

Fig. 3.—Fibrosarcomatous elements of the endometrial tumor. High-power view.



Comment

The diagnosis of carcinosarcoma of the endometrium in this case required consideration of the following: collision tumor, carcinoma with sarcomatous-like stromal reaction, inclusion of epithelial cells in sarcomatous neoplasm, and postradiation reaction. The last was excluded in view of the negative history of radiation therapy. With regard to collision tumor, the gross specimen consisted of only one polypoid mass, rather than two separate tumor entities. Microscopically, also, the two elements were closely mingled, without distinct areas of sarcoma and carcinoma. The possibility of a leiomyosarcoma colliding with an adenocarcinoma was ruled out, as the cell type appeared to be definitely fibroblastic, and the cytoplasm, with the PTA stain, failed to show myofibrils. An adenocarcinoma accompanied by sarcomatous-like stromal re-

action was excluded on the basis of the following criteria: 1. The sarcomatous cells were morphologically consistent with malignant fibroblasts. 2. There were no mononuclear histiocytes, giant cells, or bizarre fibroblasts, so commonly seen in a sarcomatous-like stroma, and no granulation tissue or granulomatous lesions. 3. Finally, the sarcomatous change was present in all areas studied, not only in the areas of carcinomatous invasion but also in fields in which malignant stroma existed alone.

In view of the criticisms of Saphir and Ewing,[8,9] the diagnosis of carcinoma with transitional sarcoma-like elements was considered, but was eliminated after detailed study. The essential morphology of the stromal cell was without question that of a malignant fibroblast. The fiber stains show the cytoplasm of individual cells to be collagenous in nature, indicating that they do not arise from the epithelial elements. On the other hand, the definite malignant nature of the epithelial elements rules out the possibility that these are normal glands trapped in an enveloping stromal sarcoma. It must be concluded, therefore, that this malignant neoplasm is composed of carcinomatous and sarcomatous cells, both of which took origin from the endometrium, and is a true carcinosarcoma.

Of the prime interest in this case is the prolonged estrogen therapy for 11 years, with continuous daily administration for 7 years. There is reliable evidence that in animals estrogens may predispose certain tissues, especially the breast, to the development of neoplasia. Such evidence is not conclusive with reference to endometrial carcinoma. However, the development of an endometrial glandular and stromal malignancy in this case and the extended estrogen therapy must be more than coincidental. The proliferation and eventual malignant change in both endometrial cellular elements could be related to this agent. The use of prolonged estrogen therapy and the development of cancer of the endometrium has been reported previously.[22] Novak and Yui[23] stated that not only are adenocarcinoma and glandular hyperplasia frequently found together, but, in many instances, one may see grades of transition, from a benign to an obviously malignant histological picture. Other authors doubt the importance of estrogen stimulation in the causation of endometrial malignancy.[24,25] Cianfrani[32] reports eight cases of endometrial cancer occurring on the average of 10.6 years after bilateral oophorectomy. He has found 7 other cases in the literature, making 15 in all. These findings imply that the ovaries or ovarian estrogens have no relationship to endometrial cancer. However, such a sweeping generalization overlooks individual factors, the prolonged latent period between neoplastic conditioning of the endometrium and the actual appearance of the tumor, other sources of estrogen-like compounds in the castrate, and the reported relationship of granulosa-cell tumors to endometrial cancer. Our case certainly strongly suggests a relationship of endometrial neoplasia to extrinsic estrogens. The fact that the patient was approximately 10 years younger than the average age group (54.1 years)[10] of this uncommon malignancy is an added reason for considering the estrogen therapy as etiologically significant.

In reviewing this case, and other reports as well, certain features in regard to the problem of carcinosarcoma have led us to a better understanding. This type of endometrial tumor is rare, more so than the literature leads one to believe. It is also presumed that, as the microscopic structure of complex endometrial tumors is studied with greater proficiency, the diagnosis of true carcinosarcoma will be made more infrequently. In agreement with other authors, we are of the opinion that there are probably only about 50 authentic cases of uterine carcinosarcoma. Secondly, numerous synonyms for this class of uterine tumors have added to the confusion. Though other classifications have been set forth,[7,29,30] we have employed the following:

A. Mesodermal mixed tumor: Tumor containing differentiated and anaplastic tissues of mesodermal origin, including cartilage, smooth muscle, and epithelial structures.

B. Carcinosarcoma: An intimate mixture of carcinomatous and sarcomatous elements but lacking multipotential derivatives or extensive metaplastic changes.

C. Teratoma: Tumor composed of elements derived from the embryonal totipotent cells. These elements usually do not (or cannot) be derived by metaplasia from tissues in the organ, i. e., teeth, nerve tissue, thyroid, etc.

The pathologist, in diagnosing such a uterine carcinosarcoma, should alert the clinician to the universally poor prognosis.[31] The treatment usually requires radical surgical removal. Radiation therapy appears relatively ineffective.

Summary

A case of endometrial carcinosarcoma in a 43-year-old woman, who received estrogen therapy for an 11-year period, is presented. Also included are a review of the literature and a brief discussion of the possible relationship of estrogens to endometrial tumors.

Laboratory of Surgical Pathology, New York Medical College, Flower and Fifth Avenue Hospitals (Dr. Speer).

REFERENCES

1. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863, Vol. 2, p. 182.

2. Läwen, A.: Über ein Rhabdomyosarkom des Uterus mit drüsigen Wucherungen, Beitr. path. Anat. 38:177-206, 1905.

3. Borst, M.: Echte Geschwülste, in Pathologische Anatomie, edited by K. A. L. von Aschoff, Jena, G. Fischer, 1928, Vol. 1, p. 653.

4. Herxheimer, G.: Über das Carcinoma sarcomatodes und einen einschlägigen Fall des Oesophagus, Beitr. path. Anat. 44:150-176, 1908.

5. Herxheimer, G.: Über das Carcinosarkom des Oesophagus, Centralbl. allg. Path. u. path. Anat. 29:1-6, 1918.

6. Krompecher, E.: Über die Beziehungen zwischen Epithel und Bindegewebe bei den Mischgeschwülsten der Haut und der Speicheldrüsen and über das Entstehen der Karzinosarkome, Beitr. path. Anat. 44:88-149, 1908.

7. Meyer, R.: Beitrag zur Verständigung über die Namengebung in der Geschwulstlehre, Centralbl. allg. Path. u. path. Anat. 30:291-296, 1919.

8. Ewing, J.: Neoplastic Diseases, Ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 286.

9. Saphir, O., and Vass, A.: Carcinosarcoma, Am. J. Cancer 33:331-361, 1938.

10. Frankl, O.: Über Koinzidenz und Interferenz von Uterustumoren: III. Carcinom und Sarkom, Arch. Gynäk. 124:67-76, 1925.

11. Goodfriend, M. J., and Lapan, B.: Carcinosarcoma of the Uterus, New York J. Med. 50:1139-1141, 1950.

12. Dixon, C. F., and Dockerty, M. B.: Carcinosarcomatodes of the Uterus, Am. J. Obst. & Gynec. 39:128-132, 1940.

13. Chesky, V. E.; Dreese, W. C., and Hellwig, C. A.: Uterine Mixed Tumor of Nine Years' Duration, Am. J. Surg. 84:721-727, 1952.

14. Harvey, W. F., and Hamilton, W.: Carcino-Sarcoma: Study of Microscopic Anatomy and Meaning of Peculiar Cancer, Edinburgh M. J. 42:337-378, 1935.

15. Jaffé, R. H.: Sarco-Carcinoma of the Uterus, Surg. Gynec. & Obst. 37:472-475, 1923.

16. Lisa, J. R.; Hartmann, H.; Bayer, I., and Bonar, L. D.: Carcinosarcoma of the Uterus, Ann. Surg. 127:738-744, 1948.

17. McFarlane, K. T., and Pritchard, J. E.: Two Cases of Müllerian Carcinosarcoma, Am. J. Obst. & Gynec. 68:652-658, 1954.

18. Neal, M. P.; Horton, C. E., and Dietrich, K. D.: Carcinosarcoma of Uterus with Report of Case, South. M. J. 43:693-696, 1950.

19. Symmonds, R. E., and Dockerty, M. B.: Sarcoma and Sarcoma-like Proliferations of the Endometrial Stroma: II. Carcinosarcoma, Surg. Gynec. & Obst. 100:322-327, 1955.

20. MacFarlane, K. T.: Sarcoma of the Uterus: An Analysis of 42 Cases, Am. J. Obst. & Gynec. 59:1304-1320, 1950.

21. Hertig, A., and Sommers, S. C.: Genesis of Endometrial Carcinoma: I. Study of Prior Biopsies, Cancer 2:946-956, 1949.

22. Fremont-Smith, M.; Meigs, J. V.; Graham, R. M., and Gilbert, H. H.: Cancer of Endometrium and Prolonged Estrogen Therapy, J. A. M. A. 131: 805-810, 1946.

23. Novak, E., and Yui, E.: Relation of Endometrial Hyperplasia to Adenocarcinoma of the Uterus, Am. J. Obst. & Gynec. 32:674-698, 1936.

24. Jones, H. O., and Brewer, J. I.: Study of Ovaries and Endometriums of Patients with Fundal Carcinomas, Am. J. Obst. & Gynec. 42: 207-217, 1941.

25. Geist, S. H., and Salmon, L. J.: Are Estrogens Carcinogenic in the Human Female, Am. J. Obst. & Gynec. 41:29-36, 1941.

26. Crossen, R. J., and Suntzeff, V.: Endometrial Polyps and Hyperplasia Produced in an Aged Monkey with Estrogen plus Progesterone, Arch. Path. 50:721-726, 1950.

27. Ingram, J. M., Jr., and Novak, E.: Endometrial Carcinoma Associated with Feminizing Ovarian Tumors, Am. J. Obst. & Gynec. 61:774-787, 1951.

28. Speert, H.: Corpus Cancer—Clinical, Pathological and Etiological Aspects, Cancer 1:584-603, 1948.

29. Symmonds, R. E., and Dockerty, M. B.: Sarcoma and Sarcoma-like Proliferations of the Endometrial Stroma: A Clinico-Pathologic Study of 19 Mesodermal Mixed Tumors, Surg. Gynec. & Obst. 100:232-240, 1955.

30. Wilson, L. A., Jr.; Graham, L., Jr.; Thornton, W. N., Jr., and Nokes, J. M.: Mixed Mesodermal Tumors of the Uterus, Am. J. Obst. & Gynec. 66:718-733, 1953.

31. Klein, J.: Carcinosarcoma of the Endometrium, Am. J. Obst. & Gynec. 65:1212-1227, 1953.

32. Cianfrani, T.: Endometrial Carcinoma After Bilateral Oophorectomy, Am. J. Obst. & Gynec. 69:64-72, 1955.

Morphology of Cortical Contusions

RICHARD LINDENBERG, M.D., and ELLA FREYTAG, Baltimore

This is a presentation of the pathology of those lesions of the cerebral cortex which are caused by mechanical forces without the overlying dura being lacerated. They are bruises and, in severe cases, lacerations of the superficial parts of the brain. They are frequently not confined to the cortex but extend more or less deeply into the subcortical white matter. Regardless of these variations, all such lesions are properly called cortical contusions. If the entire dura remains intact and, therefore, the head injury is a closed one, *all* traumatic lesions of the cortex are contusions. In open head injuries, in which they also occur, they must be differentiated from the open brain wounds.

The cortical contusions have been known since the early days of pathology, and those occurring contralateral to the site of impact, called contrecoup foci, attracted much attention. The interest of the investigators, however, was mainly focused on elucidating the physical mechanism responsible for these lesions. It was not until World War I that the pathology of the contusions was studied in greater detail (Ricker,[1] Benda,[2] and others). Spatz and co-workers[3-9] pointed out the gross and microscopic characteristics of the contusions essential for identification of the lesions and for differentiating them from lesions of vascular origin. Spatz found out that the cortical lesions in *état vermoulu* (P. Marie[10]), which were considered to be sequelae of cerebral arteriosclerosis (Dougherty,[11] Klarfeld,[12] Kodama,[13] Hassin,[14-15] and others), actually are contusion foci in their terminal, cystic phase. Another cystic condition of the cerebral cortex which he and Mittelbach[16] had formerly described as *Schizogyrie* was later identified also as the end-phase of contusion by his co-worker Riederer von Paar.[17] Rand and Courville[18-24] grossly differentiated three groups of cortical contusions: (1) the wedge-shaped, (2) the superficial, and (3) the diffuse contusions. In addition, they devoted a series of articles to the histologic changes of the various tissue constituents in contused areas. The most recent article on the subject is a comprehensive survey by Peters[25] in "Handbuch der speziellen pathologischen Anatomie und Histologie."

The present paper is intended to give a review of the subject for the general pathologist, who so often is asked for an opinion in head trauma cases. It will be supplemented by personal experiences gained from the evaluation of about 650 cases of head trauma, collected at the Office of the Chief Medical Examiner of the State of Maryland.

A large percentage of cortical contusions consists of a combination of hemorrhage and tissue necrosis. However, the hemorrhages often occur without necrosis, and, on the other hand, necroses may develop with no or only minor hemorrhage. As will be shown later, both types of lesions originate at the moment of the impact and must be considered independent, primary sequelae of the impact forces. Therefore, they will be described separately, the hemorrhages first.

Submitted for publication July 19, 1956.

The study reported in this paper was conducted under a research contract with the Army Chemical Corps.

From the Division of Legal Medicine, University of Maryland School of Medicine, and the Central Anatomic Laboratory of the Maryland State Department of Mental Hygiene.

Contusion Hemorrhages

Gross Description

The fact that this type of lesion originates at the moment of impact (Spatz,[5] Peters [8,25]) can easily be demonstrated in cases of instant traumatic death. A gunshot case may serve as an example. On its path through the temporal coronal plane, the bullet caused immediate death by destroying the hypothalamus. The sudden displacement of brain tissue led to contusions of the frontal lobe (Fig. 1). The resulting hemorrhages, although small, show certain features oftenest encountered in contusion. They are (1) located at and near the crest of the convolutions and are (2) streak-like, (3) multiple, and (4) densely arranged. This picture is so characteristic of contusion that it justifies the diagnosis of head trauma without additional proof.

Fig. 1.—Multiple, streak-like, and densely arranged contusion hemorrhages in the frontal lobe due to sudden displacement of brain tissue by a bullet passing through the hypothalamus. Instant death.

In other instances, the hemorrhages are not as numerous and as densely arranged as in Figure 1. They may occur in small groups of individual hemorrhages. Figure 2 shows three streak-like hemorrhages in the cortex of the hippocampal gyrus opposite the tentorial edge. Sometimes even solitary hemorrhages may occur, often located at the convolutional crest, but occasionally in the cortex facing the sulcus. If the hemorrhages involve the outer layers of the cortex, they are usually associated with subarachnoid hemorrhage. If they occupy the deeper cortical layers, a subarachnoid hemorrhage may be absent and the traumatic damage will become evident only after sectioning of the brain.

Within the first hours after the trauma the hemorrhages usually enlarge in size. If they are combined with contusion necroses, they often penetrate the softened necrotic tissue, but usually do not expand into the surrounding normal tissue. Because of the wedge shape of the contusion necrosis on cross section, such hemorrhage often covers a triangular area, extending into the white matter. It may have a massive appearance, as if derived from a single vessel. Histologic examination, however, will reveal its origin from several independent bleeding points. If not associated with contusion necroses, the hemorrhages stay more or less within the limits of the cortical band, similar to hypertensive ball hemorrhages. If a larger artery is damaged or if arteriosclerotic or hypertensive vascular changes are present and the blood pressure is elevated, the hemorrhages may enlarge very rapidly and the bleeding may be profuse. The final intracerebral hematoma may resemble an apoplectic one in its uniformity and destructive expansion into the white matter, into the adjacent cortex, or into the subarachnoid space. Since the rate of bleeding evidently varies from case

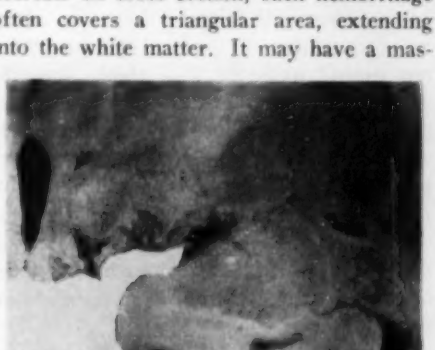


Fig. 2.—Group of individual hemorrhages (arrow) in the hippocampal gyrus due to contusion by the tentorial edge. Survival 15 days.

to case, the amount of hemorrhage in any given case does not indicate how long the patient survived.

With longer survival, the hemorrhages undergo the usual changes of their color and become smaller with progressing resorption. Hemorrhage within a contusion necrosis causes a yellow-brown pigmentation of the resulting tissue defect. Independent small hemorrhages leave inconspicuous, rust-brown spots, which are easily overlooked. Larger, independent hemorrhages are absorbed much slower. They are surrounded by a narrow zone of necrotic tissue, resulting from compression of capillaries of the border area by the hemorrhage. In the distal supply area of the bleeding artery, not involved by the hemorrhage, necrosis of the more sensitive tissue elements, resulting in a glial scar, may be observed; however, a necrosis of *all* tissue elements, leading to a softening, is rare. The cysts which constitute the terminal phase of such larger hemorrhages are usually smooth-walled and contain no or only a few structural elements. Solid connective tissue scars are rare with contusion hemorrhages. They are more characteristic of open brain wounds.

Microscopic Description

The very early hemorrhage shows a rather typical picture. The vessel in its center may be a small artery, a precapillary, or a small vein. It is collapsed and, on longitudinal section, shriveled (Fig. 3). Its perivascular space is filled with red cells over a considerable distance, explaining the streak-like gross appearance of the hemorrhage. In a lesion in which the hemorrhages are densely arranged, the capillaries participate in the bleeding, either because of mechanical damage of their walls or because of congestion resulting from the enlargement of the arterial and venous hemorrhages. A solitary hemorrhage, however, usually derives from a small artery or vein, and not from a capillary. That these hemorrhages are due to direct traumatic disruption of small arteries and veins has been demonstrated by Krauland[26] and Peters.[25] Such tears, however, are difficult to find because the bleeding vessel is collapsed and the surrounding hemorrhage usually makes identification of a defect in the vessel wall impossible.

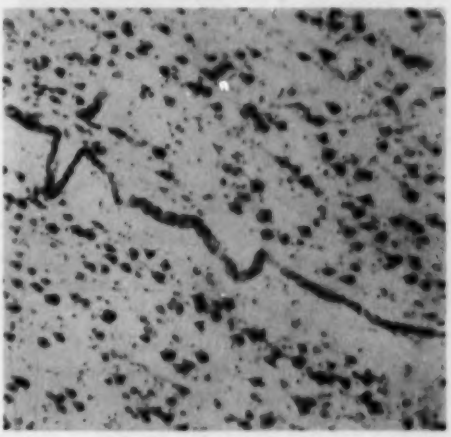


Fig. 3.—Collapsed and shriveled small artery surrounded by fresh blood (not stained) filling the perivascular space. Instant death. Nissl stain.

In the very early phase, there is little or no hemorrhage into the nerve tissue proper, and the dilatation of vessels is rare, as has also been pointed out by Spatz and Peters. The expansion of the hemorrhage with increasing survival time depends not only on type and caliber of the torn vessel but also on the extent of coincident tissue necrosis. Within a contusion necrosis, the red cells diffusely permeate the softened tissue in a more or less irregular fashion and surround the necrotic nerve cells. The larger vessels, especially the veins, may become dilated. This dilatation has been interpreted as vasoparalysis (Scheinker and Evans[27,28]) but is, in our opinion, usually due to congestion in vessels the walls of which are undergoing progressive necrosis, while the feeding arteries are generally not obstructed. Sometimes, leukodiapedesis may be observed. It is usually restricted to occasional vessels.

If the tissue adjacent to the hemorrhage is not necrotic, it first becomes compressed by the enlarging blood mass. The nerve cells become deformed and elongated

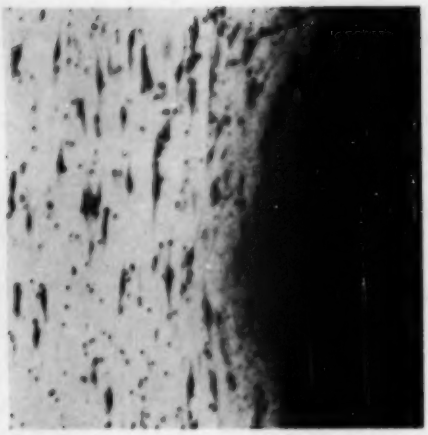


Fig. 4.—Solitary contusion hemorrhage exerting pressure on the intact nerve tissue. Elongation and deformation of nerve cells. Survival one hour. Nissl stain.

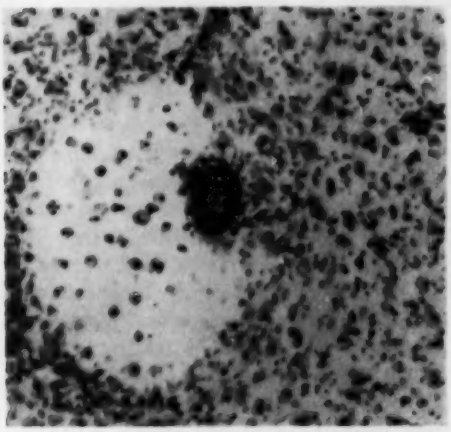
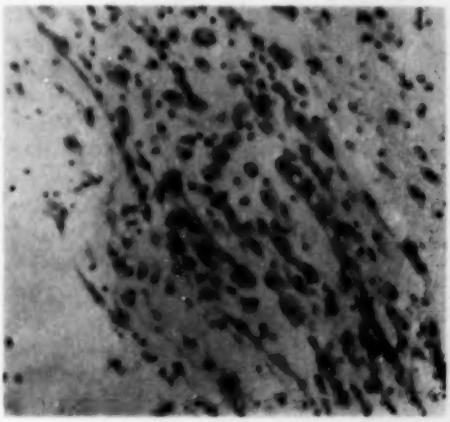


Fig. 5.—Larger perivascular contusion hemorrhage causing pressure on nerve tissue. Marked progressive changes of perivascular glia. Delayed resorption of hemorrhage. Survival one month. Nissl stain.

(Fig. 4) without being surrounded by red cells. If the pressure exerted by the hemorrhage interferes with capillary circulation in the marginal zone, the nerve cells will selectively die, while the glial cells survive and undergo progressive changes. If the marginal hypoxia is more pronounced, a necrosis of all ectodermal elements, in other words, a marginal softening, develops. Further bleeding into the softened area may enlarge the hemorrhage hours, or even several days, after the original accident.

The early signs of resorption of a small hemorrhage may be observed 24 to 48 hours after the accident. If the hemorrhage has remained in the perivascular space rather than dissected into the brain tissue, the resorption is achieved by phagocytic activities of the adventitial cells and is often accomplished within a few days. If the hemorrhage has exerted pressure on the otherwise intact nerve tissue, the perivascular glia may develop marked progressive changes, which are most obvious in the astrocytes (Fig. 5). These glial changes do not reliably indicate the histologic age of the hemorrhage because they are a response to the hypoxia caused by the enlargement of the hemorrhage, which may not have taken place until quite some time after the accident. If the hemorrhage has penetrated the nerve tissue but remains small, the resorption takes place by perivascular elements within the hemorrhage, as well as by microglial phagocytes in its periphery. Larger hemorrhages are mainly resorbed from the periphery by microglia cells and mesodermal phagocytes deriving from proliferating capillaries of the marginal necrotic zone (Fig. 6). Whatever the manner of resorption may be, its rate varies from

Fig. 6.—Larger contusion hemorrhage which penetrated into the nerve tissue, in phase of resorption by peripheral mesodermal and microglial phagocytes. Survival eight days. Nissl stain.

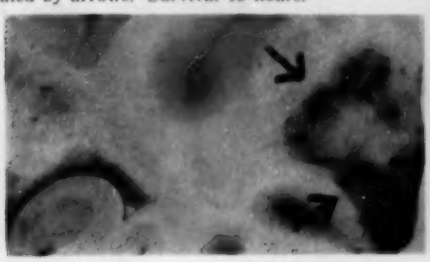


lesion to lesion and is obviously dependent not only on the size of the hemorrhage but also on variations in its composition. For this reason, it is difficult to estimate the age of a hemorrhage from the intensity of phagocytic activity and from the reaction of the surrounding tissue.

Fig. 7.—Old, cystic contusion foci of different sizes typically involving the crest of the convolutions. Frontal lobe.

Fig. 8.—Three wedge-shaped contusion necroses interspersed with hemorrhages at the crest of the temporal convolutions. Survival 10 hours.

Fig. 9.—Almost ischemic, recent contusion necrosis demarcated from the surrounding tissue by gelatinous appearance. The demarcation is indicated by arrows. Survival 15 hours.



Contusion Necroses

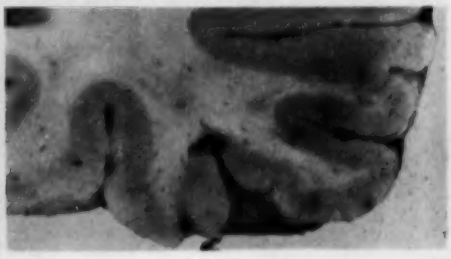
Gross Description

On examining the surface of the brain, one finds difficulty in determining the extent of contusion necrosis in recent injuries because the lesions are usually covered by subarachnoid hemorrhages. They present themselves easily in old cases, as shown in Figure 7, where they are circumscribed, crater-like defects or resemble open trenches or furrows similar to accessory sulci. This is the condition which Pierre Marie had called *état vermoulu* and which was once believed to be caused by arteriosclerosis.

On cross sections through early lesions, the site of contusion necrosis is usually indicated by hemorrhages, but the exact shape and extent of necrosis can often not be recognized until 10-12 hours after the accident, unless the hemorrhages have enlarged and have diffusely stained the necrotic area (Fig. 8). If this is not the case, or if the necrosis is ischemic, the first alteration which can be noticed is a slight swelling of the necrotic tissue, accompanied by a gelatinous appearance. Because of this change the lesion becomes demarcated from the intact surrounding area (Fig. 9).

During the first five to seven days the necrotic tissue shows a mild increase in size. Then the swelling recedes and the necrotic tissue becomes friable. It is gradually re-

Fig. 10.—Very small, but typically wedge-shaped contusion cyst at the crest of the convolution (arrow). Small cortical defect at floor of sulcus due to solitary hemorrhage. Survival unknown.



sorbed, and in four to six months the lesion becomes cystic. Because of the accompanying hemorrhage the cyst shows yellow discoloration, sometimes lasting for years. It is characteristic that no scar tissue develops within the cyst and that it is broadly communicating with the subarachnoid space.

The majority of the contusion necroses are wedge-like in shape on cross section. The angle of the wedge may vary, but its base is always at the crest of a convolution and its point is directed toward or into the white matter. Therefore, the cortex around the sulci is characteristically spared (Figs. 8, 9, and 25), although it may be involved if the lesion is large and extends over two or three convolutions. Regardless of size, the large lesions are usually also wedge-shaped. Even very small, old foci can be grossly identified by this typical configuration (Fig. 10). Also, in the cerebellum, most of the cortical contusion necroses are triangular in spite of the rich foliation of the cerebellar surface.

Rarely, contusion foci have a more dish-like appearance or may be almost rectangular. This is often the case with lesions in the caudal orbital lobe or the temporal pole facing the small sphenoid wing. These shallow lesions have been described as "superficial contusions" by Rand and Courville.[21]

Microscopic Description

In cases of death at the time of the accident there are no changes which would convincingly indicate the presence or the extent of a contusion necrosis. The only alteration

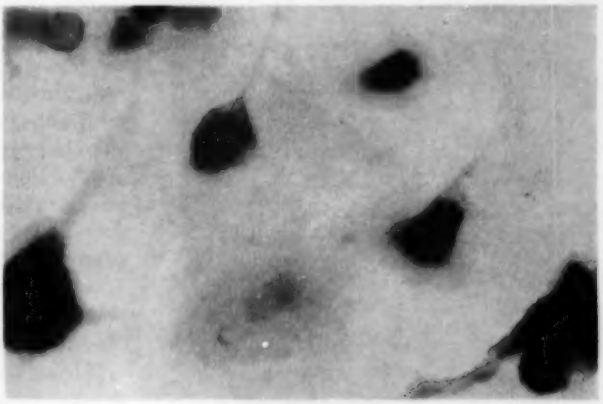


Fig. 11.—Instant death due to gunshot (same case as that in Figure 1). Severe shrinkage of nerve cells at the crest of the convolutions, where multiple hemorrhages are present. Nissl stain.

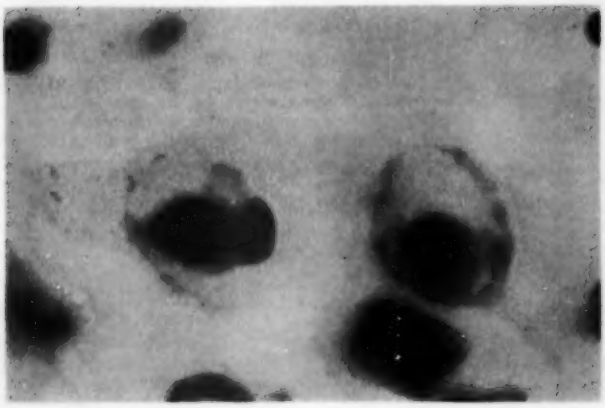


Fig. 12.—Same case as in Figures 1 and 11. Postmortem swelling and vacuolation of nerve cells from an area adjacent to the contused one. Nissl stain.

which can be observed is an acute shrinkage of nerve cells in an area in which tiny contusion hemorrhages suggest the presence of contusion necrosis. The cellular shrinkage becomes more striking if in the other areas of the cortex the nerve cells develop postmortem swelling and vacuolation (Lindenberg [29]). Figure 11, from a case of instant death (gunshot), shows such a severe shrinkage of nerve cells at the crest of a convolution with multiple contusion hemorrhages, as seen in Figure 1. Figure 12 (from the same case) shows postmortem swelling and vacuolation of the same type of nerve cells from an area adjacent to the contused one. There is a rather sudden transition from the area of cellular shrinkage to that of swelling. Since the acute shrinkage is not a specific alteration, it cannot, per se, be taken as a sign of contusion. However, when the shrinkage is limited to an area of contusion hemorrhage and is more or less sharply demarcated from areas of postmortem cellular changes, the conclusion may be justified that contusion necrosis is present.

If the lesions are survived for three to five hours, definite signs of necrosis can be found. In Nissl stains the necrotic cortex and white matter are paler than the normal tissue. A thin demarcation line may be visible. It is usually more apparent in myelin sheath preparations (Fig. 13). This demarcation line indicates the final extent of that necrosis which is directly caused by the impact. With increasing age, the tissue immediately beyond the demarcation line often undergoes necrobiotic changes, but the cellular reactions are different from those within the necrosis proper. They are especially helpful in estimating the age of the lesion. It is for this reason that in the following description of lesions of various age groups the focus proper and the border zone area will be dealt with separately. Rand and Courville [19,21] also differentiated certain zones of cellular reaction in a contusion but did not mention the demarcation line. Their first zone of immediate destruction apparently is equivalent to the zone of contusion necrosis proper. The other zones, of secondary or delayed disintegration, of reversible reaction, and of reactive gliosis, obviously correspond to our border zone.

Focal Area Proper.—The time sequence of the histologic changes occurring in the focal area proper will be described first.

The phase of active necrosis is characterized by a progressive paling of the focal area, best noted with low power in slides stained by the Nissl method. As has been mentioned before, this paling starts as early as 2 to 3 hours after the trauma and is fully developed within 12 to 48 hours. Figure 14 shows two adjacent lesions in which the cortex and white matter show the same degree of paleness, due to a loss of staining

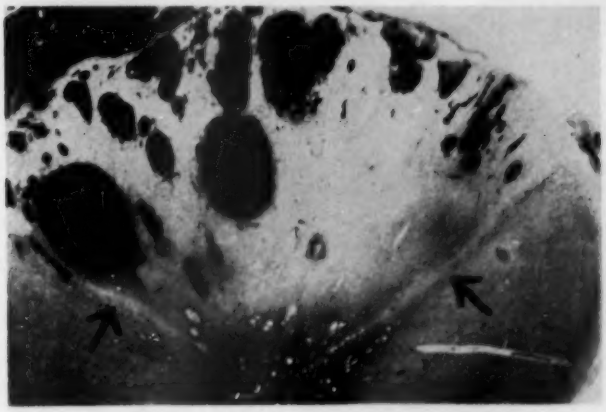


Fig. 13.—Thin demarcation line between contused area and normal tissue (arrows). Survival three hours. Myelin sheath stain.

Fig. 14.—Paleness of cortex and white matter of two contusion foci with Nissl stain. Survival two days.

properties of the cellular elements. Under higher power, within as little as three to five hours the initially dark and shrunken nerve cells stain lighter, owing to a homogenization process in their protoplasm with lysis of the tigroid substance. Their nuclei are small and dark, often triangular in shape. The nuclei of glial and mesodermal elements are pyknotic. At this age, all nerve cells within the focal area show practically the same degree of alteration. The demarcation line (Fig. 13) belongs also to the necrosis proper. It is visible as such because of a mild edema, which widens the intercellular spaces. Swelling and vacuolation of nerve cells, as well as incrustations of the pericellular structures, are rare in the necrosis proper.

Within the following hours of survival the rate of cellular desintegration may vary to some extent from one area of the lesion to the other. It is often slower near hemorrhages than in ischemic portions of the focus. This is illustrated in Figures 15 and 16 from a 21-hour-old contusion. In Figure 15 the bodies of the nerve cells can still be recognized in spite of marked homogenization. In Figure 16 small, pale, and somewhat egg-shaped nuclei are all that is left of the nerve cells in another area of this lesion. The glial nuclei are still pyknotic, but they, too, will become gradually paler. It is important to note that the glial cells of the first cortical layer also undergo necrosis. Occasionally, one may find in some parts of the lesion an invasion by polymorphonuclear leukocytes, which do not contribute in any way to the resorption of the lesion because they, too, die. Once the phase of necrosis is complete, it may persist unchanged for several weeks without any signs of active phagocytosis except for occasional compound granular cells, originating from local, surviving microglial or

Fig. 15.—Disintegration of nerve cells in a contusion necrosis. Bodies of nerve cells still visible near hemorrhage. Survival 21 hours. Nissl stain.

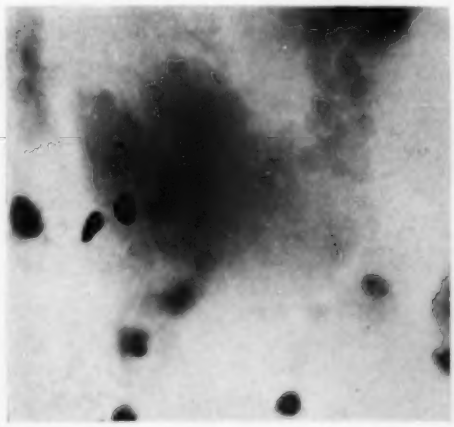


Fig. 16.—Same case as in Figure 15, but different area of the contusion necrosis. Two pale, egg-shaped nuclei left as remainder of nerve cells. Nissl stain.

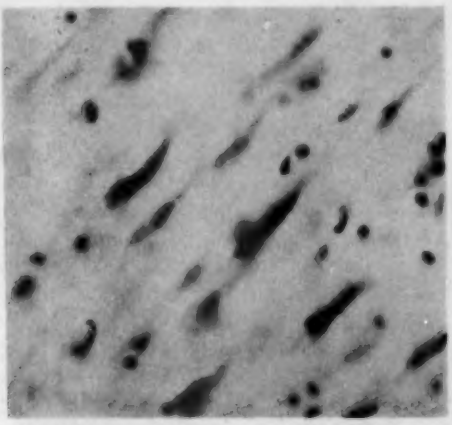


Fig. 17.—Bizarre deformation and early necrosis of nerve cells of the border zone near the demarcation line due to pressure exerted by an enlarging, four-hour-old contusion necrosis. Nissl stain.

vascular elements. The progressive reaction of the vascular elements characteristic of ischemic softening, i. e., colliquative necrosis, is conspicuously absent.

The actual resorption of dead tissue is achieved not from within the lesion but by cellular elements of the border zone and of the subarachnoid tissue. In this, the contusion necrosis behaves similarly to a coagulative necrosis of vascular origin.

Border Zone.—The border zone includes cortex and white matter beyond the demarcation line, the remainder of the first layer of the cortex, and the leptomeninges covering the outer surface of the contusion necrosis. Within the cortex and the white matter, the width of the border zone and the intensity and rate of the cellular changes vary to some extent from lesion to lesion, apparently depending on the rate and intensity of hypoxia caused by the pressure exerted on the border tissue by the enlargement of the lesion during the first few days. None the less, the general pattern of the reaction is always the same. As an example, the histologic changes in middle-sized contusion necroses associated with hemorrhages may be described, according to age of the lesion. The tissue around three- to five-hour-old lesions shows rows of shrunken or homogenized, elongated nerve cells, closer together than normal. The cells nearest the demarcation line may exhibit bizarre deformation, as shown in Figure 17. The nuclei of the glia and of the cellular elements of the vessels are somewhat pyknotic. There is a gradual transition from this zone of compression to the normal tissue. During the next few hours the nerve cells closest to the necrotic area begin to show incrustations of their pericellular structures, as seen in Figure 18. The more peripheral nerve cells of the border zone maintain more or less their shrunken, compressed appearance. The glial and mesodermal nuclei, including those of the leptomeninges, often show severe pyknosis.

In 12- to 24-hour-old lesions incrustations of the pericellular structures, especially of middle-sized and large pyramidal cells,

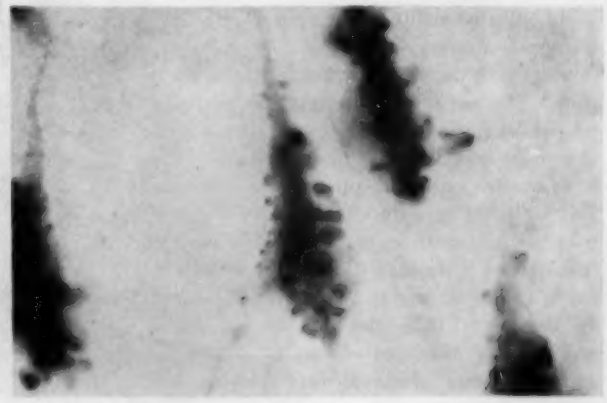


Fig. 18.—Incrustations of pericellular structures of nerve cells in the border zone of a 21-hour-old contusion necrosis. Nissl stain.

Fig. 19.—Early progressive changes in form of swelling of nuclei of vascular-cell elements in border zone of two-day-old contusion necrosis. Nissl stain.

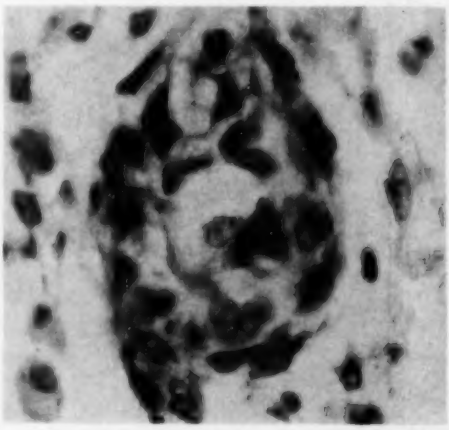
is a common finding near the necrotic area. Almost all nerve cells are more or less shrunken, but occasionally there are enlarged cells, usually showing vacuolation and homogenization. Glial and mesodermal nuclei still show regressive changes. The capillaries are better visible because they appear wider and are filled with amorphous, proteinaceous fluid.

The same picture continues without major change until the lesion is approximately 36 to 48 hours old. At this time, initial progressive changes in the form of swelling of nuclei can be observed in the mesodermal cells of the leptomeninges and of the perifocal capillaries (Fig. 19). The nuclei of the astrocytes and of the microglia in the adjacent cortex and white matter react similarly. Occasionally, a few gitter cells deriving from microglia may be present, especially in the white matter of the border zone. The nerve cells nearest the necrosis proper continue to display incrustations and shrinkage and are still fairly stainable.

With the onset of progressive changes and with the appearance of the first gitter cells, the phase of necrosis gradually passes into that of resorption during the following days. In lesions two to four days old, many of the nerve cells close to the necrosis proper have disappeared, while microglia and astrocytes show further progressive changes. There is increasing formation of single gitter cells by individual microglial cells. The nuclei of the mesodermal cells of the capillaries become large and juicy and may show beginning proliferation. The subarachnoid tissue over the focal area often produces large numbers of histiocytes, which migrate into the necrotic first layer of the cortex and form compound granular cells. Some of the microglial cells of this layer may recover and participate in the phagocytosis.

During the fourth to the seventh day, the most obvious change is a marked proliferation of the endothelial and perithelial cells of the vessels. The most peripheral cells of the vessels separate and become macrophages (Fig. 20). The number of microglial cells increases, and these cells migrate into the necrosis proper and participate in the phagocytosis. Therefore, along the margin of the necrosis the number of compound granular cells grows steadily, especially in the white-matter portion of the border zone and in the first layer of the focus. Nerve cells, mostly shrunken, are present only in the peripheral portion of the border zone, accompanied by astrocytes showing some progressive change. The nerve cells closest to the focus proper have completely disappeared, as did the oligo-

Fig. 20.—Formation of macrophages from mesodermal cells in the border zone of a seven-day-old contusion necrosis. A few microglial gitter cells are present. Nissl stain.



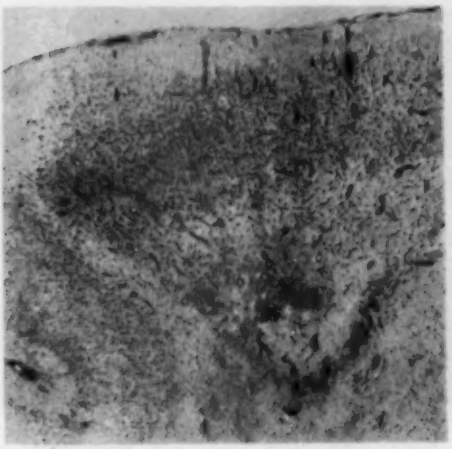


Fig. 21.—Marked proliferation of vascular and glial cell elements in border zone of a nine-day-old contusion necrosis. Nissl stain.

dendroglia cells and some of the astrocytes. A local accumulation of polymorphnuclear leukocytes may be observed. Occasionally, there may be some infiltration of small segments of the border zone by plasma cells and lymphocytes. The astrocytes of the remaining portion of the first cortical layer near the margins of the focus show marked progressive changes with formation of gemistocytic cells and *Glia-rasen*.

During the second week proliferation of phagocytes continues. They migrate from the border zone into the peripheral zone of the necrotic area proper. The number of compound granular cells increases steadily, most markedly in the white-matter portion of the lesion and in the superficial portion of the cortex. In the cortical portion of the border zone, the microglial cells and macrophages are markedly increased and crowd the spaces between the capillaries. Figure 21 shows, on a tangential section through the border zone, the marked proliferation characteristic of this phase. It is of interest to note that the granulation shows a rather distinct border toward the preserved cortex and white matter. Occasionally, the proliferation of vessels may give cause to delayed hemorrhages within the border zone. Where intrafocal hemorrhages are close to this zone, fibroblasts are sprouting into the blood, and phagocytes, sometimes giant-sized, are resorbing it from the periphery. The same takes place with hemorrhages in the cortex near the subarachnoid space.

In lesions two to four weeks old, the proliferation of phagocytes continues at a slower pace, but in some areas of the cortical border zone the granulation may become very dense and local accumulation of plasma cells may occur. Migration of phagocytes into the necrosis proper continues. At the end of the fourth week, the proliferation of cells seems to cease.

During the following two months, the phagocytes which had migrated into the necrosis proper slowly break down the dead tissue, starting at its periphery. Thus, the core of the lesion is surrounded by an ever-growing wall of compound granular cells

Fig. 22.—Wall of compound granular cells surrounding the coagulated core of an approximately three-month-old contusion necrosis. Nissl stain.

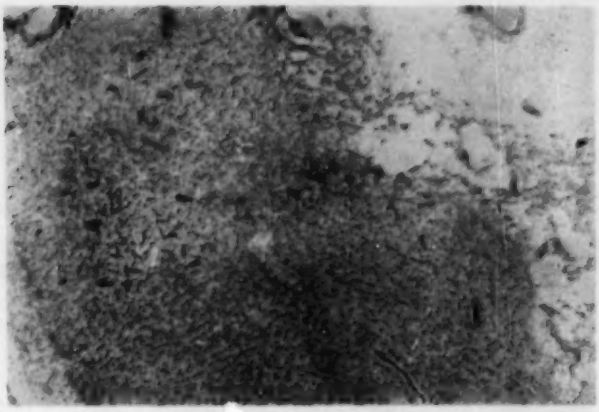


Fig. 23.—Cortical border zone of a six-month-old cystic contusion. Loose network of connective tissue within the cyst. Intense staining of vessels in border zone as after-effect of former proliferation. Nissl stain.

(Fig. 22). At the same time, the formation of an "accessory pia-glia membrane" takes place along the border of the perifocal tissue.

With survival longer than three months, not only are the last remnants of necrotic tissue removed by the phagocytes but also the compound granular cells gradually disappear, either by lysis or via the subarachnoid space. Since the resorption of the necrotic tissue takes place by individual phagocytes migrating into the dead tissue and not by proliferation of vessels within the necrotic area, the resulting cyst is devoid of the vascular network which is so characteristic of a cystic vascular softening. Such a network, if found at all, is near the border zone of the contusion cyst. It may harbor a few remaining gitter cells, which often contain iron pigment. Esser [30] erroneously interpreted the presence of these gitter cells as indicative of a chronic tissue process still continuing, even in older lesions. Figure 23 shows the cortical border zone area with adjacent network within a cystic, six-month-old lesion. The border zone itself is relatively wide and consists mainly of glial scar tissue. Some of its vessels are dark-stained because the number of their lining cells is still increased as an after-effect of the proliferation phase. At higher power, one can also occasionally see fixed compound granular cells within the glial scar tissue. Not infrequently the darkly stained, preserved bodies of dead nerve cells incrusted with iron pigment (Rand and Courville [22]) may be found within the border zone. They stain almost black with hematoxylin. Figure 24 represents the cortical border zone area in a six-year-old contusion. The marginal network and the glial scar of the border zone still contain nests of iron-storing compound granular cells. The arrow in the Figure

Fig. 24.—Cortical border zone of a six-year-old contusion cyst. Glial scarring in cortex. Phagocytes storing iron pigment within the scar and within the marginal network of the cyst appear as black globules. Arrow points to remainder of first cortical layer. Nissl stain.

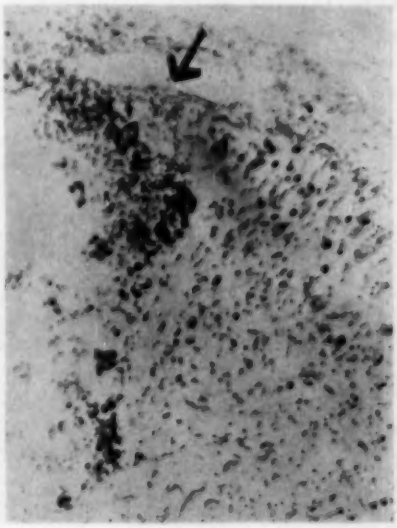


Fig. 25.—Two old contusion cysts at the crest of convolutions filled with fresh subarachnoid hemorrhage, resulting from a recent injury. Note the characteristic stumps of the first cortical layer at the margins of the old cysts (arrows). Nissl stain.

points to the short stump of the first cortical layer. Since this layer is completely dissolved over the center of the cyst, the cystic cavity is in open communication with the subarachnoid space. This is better demonstrated in Figure 25, in which a subarachnoid hemorrhage originating from a head injury three hours before death fills not only the subarachnoid space of a sulcus but also the cavities of two old contusion cysts resulting from a former head trauma. In this Figure the characteristic stumps of the first cortical layer (arrows) may also be noted.

Differential Diagnosis

Contusion Hemorrhages.—The differential diagnosis of the contusion hemorrhages will be discussed first. In regard to *solitary* traumatic hemorrhages of the cortex, there is only one type of nontraumatic hemorrhage which is grossly similar. It is the ball hemorrhage, or miliary apoplexy, occurring in cases of arterial hypertension. If there is any doubt of the nature of the hemorrhage on gross examination, histologic study will establish the diagnosis. In contrast to contusion hemorrhage, the ball hemorrhage is caused by rupture of a small artery, locally dilated because of hypertensive vascular disease (Anders and Eicke[31]). Therefore, it is more round-shaped than streak-like. The artery usually still shows some dilatation after hemorrhage, whereas in a contusion hemorrhage the bleeding vessel is collapsed regardless of whether its wall is normal or degenerated due to hypertension.

The *multiple* and densely arranged contusion hemorrhages may be confused with the hemorrhages in vascular softenings very often found as secondary lesions in cases of head trauma in which contusion hemorrhages are also present. However, these two conditions can easily be differentiated, grossly as well as histologically. In softenings, the hemorrhages are seldom confined to the crest of the convolutions and appear to be more diffuse because they originate mainly from capillary diapedesis. The streak-like arrangement, so characteristic of contusion hemorrhages, does not occur in hemorrhagic softenings, and the latter rarely extend into the softened white matter, as cortical contusion hemorrhages frequently do. Figure 26 demonstrates a hemorrhagic necrosis in the supply area of the posterior cerebral artery in a case of blunt head trauma. This type of lesion should not be mistaken for a primary traumatic alteration.

Fig. 26.—Recent hemorrhagic and ischemic necrosis in the occipital lobe due to compression of the calcarine branch of the posterior cerebral artery, caused by traumatic increased supratentorial pressure. Survival four days.

It is a hemorrhagic softening often caused by compression of the posterior cerebral artery or branches by the tentorial edge, due to increased intracranial pressure above the tentorium (Lindenberg[32]). The fact that the hemorrhages in such lesions follow the cortical band along the sulci is very characteristic of their nontraumatic, vascular origin.

Diagnostic difficulties may arise when in a traumatic case with increased supratentorial pressure the tentorial edge causes a local hemorrhagic pressure necrosis in the cortex of the hippocampal gyrus. Such a lesion can hardly be differentiated from a contusion. One difference that may occur is that the hemorrhage is more diffuse and not as streak-like as in a contusion (Fig. 2) and that in cases in which the hippocampal gyrus herniated over the edge of the tentorium, the contusion hemorrhage also herniated and moved to a site medial to the tentorial edge, whereas the pressure necrosis is found opposite the edge of the tentorium.

Contusion Necroses. — There are three types of nontraumatic softenings which may cause differential-diagnostic difficulties. The first type is a total softening in the supply area of a small arterial branch involving cortex as well as subjacent white matter, as represented in Figure 27*B*. It is usually caused by an acute occlusion of the artery. Its shape may be as triangular as that of a contusion necrosis but, in contrast to the rather straight-line border of a contusion necrosis, its border is usually irregular, showing a zigzag pattern. Histologically, it differs from a contusion in that the outer portion of the first cortical layer is either totally preserved or interrupted for only a short distance. In contusion, this layer undergoes necrosis and eventually becomes resorbed except for its most peripheral portion close to the cortical border zone. A second histologic difference can be observed during the phases of necrosis and resorption. It consists in the fact that contusion necroses are more or less of the coagulative type and are resorbed from the periphery, whereas nontraumatic softenings of medium size are usually of the colliquative type and are resorbed not only from the periphery but also by phagocytes originating from intrafocal microglial and perivascular elements. The latter fact accounts for another differential-diagnostic characteristic which becomes evident once the lesion reaches its cystic phase: A cyst resulting from vascular occlusion is filled with a rather dense, spider-web-like network, the remainder of

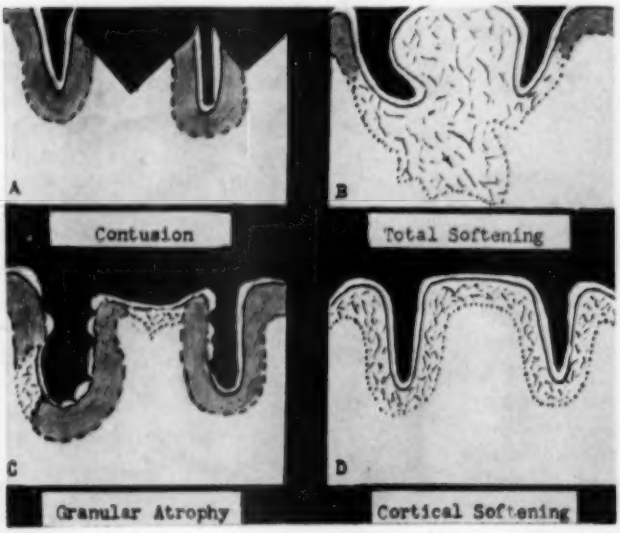


Fig. 27.—Diagrams of four types of cortical lesions.

the intrafocal capillary system; in contusion cysts such network is practically missing.

The second type of nontraumatic softening which may be confused with contusion necrosis is the so-called granular atrophy (Fig. 27*C*), as seen, for instance, in obliterative thromboendarteritis (Lindenberg,[33] Lindenberg and Spatz[34]). The granular appearance of the cortex is caused by glial scars around small intracortical arteries. Besides these scars, small softenings simulating a contusion may also develop. These softenings, in contrast to contusions, are covered by the surviving outer part of the first layer of the cortex and in their cystic phase are filled with the spider-web-like network of connective tissue.

The third type of softening which must be considered is the one in which only the cortical band becomes necrotic (Fig. 27*D*). It has already been mentioned in the differential diagnosis of contusion hemorrhages. Figure 26 shows the early phase of a hemorrhagic softening of this type. The softening, however, may be ischemic. Whether it is hemorrhagic or ischemic, it can easily be differentiated from a contusion necrosis because it equally involves the crests and sulcal portions of the convolutions and the first layer of the cortex is always preserved.

If the contusion necrosis is shallower and more dish-like in shape, as is usually the case in the cortex of the orbital and temporal lobes facing the small sphenoid wings, it may be very similar to a vascular necrosis because the first layer of the cortex may be better preserved than in the typical wedge-shaped contusion. In such cases, the location of the lesion, the possible presence of wedge-shaped contusions in its vicinity, and, in its early phase, the type of hemorrhage will help to identify it as a contusion.

Occasionally, a contusion necrosis may seem to extend unusually far into the white matter (Fig. 28). A closer analysis reveals that the original contusion necrosis has, in addition, a superimposed vascular necrosis caused by thrombosis of a contused artery. It is this vascular necrosis which extends into the deeper portion of the white matter. Here it shows the irregular outlines characteristic of a vascular necrosis.

Fig. 28.—Twelve-day-old contusion necrosis with superimposed vascular necrosis due to thrombosis of a contused artery. Note irregular border line of vascular necrosis in deeper white matter (arrow).

Finally, it is of interest that exposure of a local area of the cerebral cortex to ultrasound (Lynn and Putnam,[35] Peters[36]) or to low temperature (Balthasar[37]) also results in tissue necrosis and that the lesions may be almost identical with contusion necroses.

Pathogenesis

The contusion hemorrhages are the direct result of mechanical stress. This has been proved by the occasional finding of a tear in the vascular wall, as well as by the fact that hemorrhages occur at the moment of the impact without being preceded by vasoparalysis and stasis.

In regard to the contusion necroses, it has been suggested that they result from anoxia secondary to mechanical injury to the vascular system. Some authors believe that vasospasm and paralysis follow the injury and cause such anoxia (Ricker and Döring[38]). The fact that contusion necrosis without hemorrhages may be found could be used in favor of this theory. However, the morphologic picture of vascular stasis is uncommon within the early lesion.

Therefore, only a prolonged spastic reaction of arteries could be responsible for the tissue necrosis. If that were the case, it would be very unusual that all cellular elements, including the vessel walls, would die, as they do in contusions. Furthermore, arterial spasm would not regularly result in a wedge-shaped necrosis at the crest of a convolution but would vary greatly in shape and in extent, depending on the supply area of the artery involved.

Other authors have suggested that the hemorrhages caused by the impact lead to circulatory disorder and therefore result indirectly in tissue necrosis. Courville [21] obviously had this concept in mind when he stated that "the immediate effect of the original injury is to produce hemorrhage and that this hemorrhage is largely responsible for the extent of cortical damage." Also, this explanation is not satisfactory because contusion hemorrhages may be fair-sized without resulting in a wedge-shaped contusion necrosis, and contusion necrosis sometimes develops without significant hemorrhage.

Whatever might be considered the cause of the anoxia, lesions due to anoxia do not display the features characteristic of the contusion necroses, for instance, the destruction of the first cortical layer, the relatively straight border lines, or the lack of mesenchymal network in the cystic end-phase.

Since the characteristics of the contusion necroses cannot be explained by any anoxia theory, the question arises whether mechanical forces alone are responsible for their origin. Most of the papers which have been written on the physical aspects of head trauma are primarily concerned with the mechanism that determines the occurrence and the site of the contrecoup lesions and do not take into account the specific morphologic features of the contusion necroses. Hallervorden [39] is the first investigator who considered these in his theory of the mechanical etiology of the necroses. His theory is based on the fact that colloidal solutions may change from a sol to a gel or vice versa if exposed to mechanical stress, a phenomenon called thixotropy. He believes that in head trauma compression waves arriving and overlapping at the site contralateral to the impact area cause an irreversible gelification of the protoplasm, followed by death of all tissue elements. This theory has been accepted by Spatz.[6] In his opinion, the compression waves are reflected at the inner table of the bone, like light rays in a concave mirror, and the conical shape of the necroses may be compared with the cone formed by the reflected light. This mechanical theory best explains not only the morphologic characteristics of contusion necroses described in this paper but also the fact that in persons killed immediately by the accident the nerve cells show severe acute shrinkage as the first sign of cellular necrosis in areas of contusion (Fig. 11). For these reasons we believe with Hallervorden and Spatz that mechanical forces alone are responsible for the necrosis in cerebral contusion.

To this concept we like to record some additional observations in regard to the more detailed physical process leading to the tissue necrosis. These are based on pathologic, and not physical, observations and are therefore hypothetical in nature and liable to revision. Since the morphology of the coup lesions is identical with that of the contrecoup lesions, our considerations are first directed to the coup lesions, where the physical events appear to be less complicated and controversial than those occurring at the site of the contrecoup.

It has been proved experimentally that the skull undergoes a short-lasting elastic deformation at the moment of the impact. It is known that in a hammer blow to the unsupported head of a dog the initial, maximal deformation takes place in 1/2000 second and that after a few more, rapidly dampened oscillations of the bone an equilibrium is reached in about 1/200 second after the blow (Gurdjian and associates [40]). Depending on the intensity of the blow, the initial positive pressure may amount

to 7 atmospheres or more, constituting the sum total of the pressure caused by the bone deformation and the pressure due to the acceleration of the head, which reaches its maximum of up to 750 g a fraction of a millisecond after the initial maximal bone deformation. This impulse-type pressure will be transmitted to the convolutional crests subjacent to the area of bone deformation if the cushion of cerebrospinal fluid over the crests is significantly thin. The crests will be suddenly flattened, and, since this flattening starts at the point or line of first contact between bone and brain and spreads from there into the periphery, there will be a spreading of shearing forces within the microscopic and submicroscopic constituents of the tissues while the cortex is being compressed. If the inner table of the skull is smooth and the convolutional crest rounded, the area of maximal compression must have the shape of a wedge pointing toward the white matter, in view of the very fast development of the pressure and the inertia of the brain tissue. With the onset of the back flip of the depressed bone, this wedge-shaped area will be under some negative pressure, and probably under the influence of cavitation and reversed shearing forces. However, according to Coe and co-workers,[41] a transient, well-formed cavity does not develop. The amplitude of the second oscillation of the bone, as well as of the few following oscillations, is apparently so much lower than that of the initial one that they may be disregarded. There is pathologic evidence that of the first oscillation only the initial positive phase is essential for the occurrence of tissue necrosis. We have found a typical wedge-shaped contusion necrosis beneath a localized depressed fracture in which the fragments were arrested at the moment when the skull broke (Fig. 29). There was apparently no back flip of the bone fragments. This indicates that the initial compression of the tissue caused irreparable damage to all the tissues within the wedge-like area, including the first layer of the

Fig. 29.—Depressed fracture of inner table of skull. Fragments arrested in same position as when fracturing occurred.

cortex and the cellular elements of the vascular system. The pressure waves which emanate from the area of compression and travel through the brain at the speed of 4700 ft/sec. (Gurdjian and associates[42]) may lead to a tear of an individual vessel within the deeper portions of the brain but have no necrotizing effect upon the nerve tissues unless they meet a medium of greater consistency. When arriving at the contralateral surface of the brain, they cause an impulse-like pressure, which in experiments on dogs with blows to the unsupported head measured up to 7 atmospheres, in spite of some negative pressure due to acceleration of the head (Gurdjian and associates[40]). From this it may be theorized that a compression of the tissues, similar to that described at the site of impact, causes the contrecoup necroses if the crests of the convolutions are sufficiently close to the bone. The cortical contusions in gunshot cases described above (Fig. 1) speak in favor of this theory. Since some authors (Sjövall[43] and others) believe that the contrecoup lesions are caused not by compression but by negative pressure or cavitation, and therefore speak of tissue tears, it may be stated that in our experience and that of Spatz and Peters, original, i. e., not postmortem, tears of the nerve

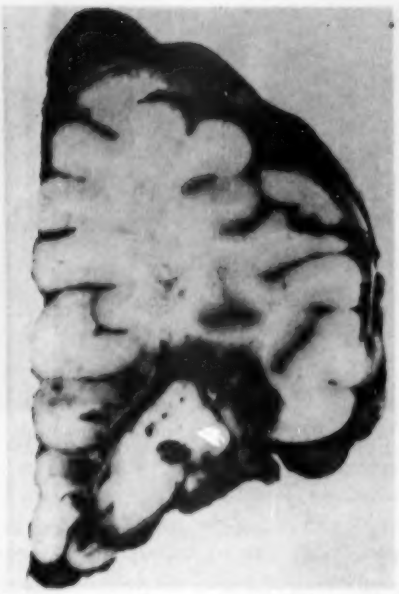


Fig. 30.—Three-hour-old, ischemic contusion necrosis wedged into the surrounding tissue and separated from it. The hemorrhages are confined to the surrounding tissue.

tissues are very rare in contusion necroses. Although a lesion may be entirely separated from its surroundings, as is seen in Figure 30, this is not necessarily due to negative forces. In this particular case the lesion is a coup lesion. The compressed, and therefore firmer, tissue was wedged into the softer surroundings, at the moment of the impact to the orbital roof as it fractured. It may be noted that the tissue wedge in this case is very pale and ischemic, whereas the surrounding tissue is hemorrhagic. This appears to have some significance. We have observed a similar phenomenon in a gunshot wound caused by a .45-caliber bullet. The tissue adjacent to the wound canal was very pale, and hemorrhages were present only peripherally from this anemic tissue. These two observations, together with the findings in other lesions, suggest that very severe compression of the tissue causes necrosis and no hemorrhage, less severe compression results in both necrosis and hemorrhage, and a still less degree of compression may result in hemorrhages without necrosis of the nerve tissue. Not only is it possible that the compression with its accompanying shearing forces is responsible for the tissue necrosis, but the sudden compression may also generate heat which may contribute to the coagulation. To our knowledge, the possible significance of heat as additional factor for contusion necrosis has never been mentioned and needs to be experimentally investigated.

Summary

Cortical contusions are those bruises and lacerations of the surface of the brain which are covered by an intact dura.

The tissue alterations caused by contusion of the cortex are subdivided into hemorrhages and necroses, which may occur independently of each other. Both alterations originate at the moment of impact and predominantly involve the crests of the convolutions. The contusion hemorrhages may be solitary but are mostly multiple, streak-like, and densely arranged. The contusion necroses are usually wedge-shaped on cross section, the point of the wedge extending toward or into the white matter. Since usually all ectodermal and mesodermal elements within the lesion undergo necrosis, the contusion necrosis is similar to a coagulative necrosis; i. e., its resorption takes place from the peripheral border zone. For the same reason, the resulting cystic defects are void of the spider-web-like network of the surviving vessels within the lesion, so characteristic of old colliquative necroses. Since the first layer of the cortex participates in the necrosis, the cystic lesions openly communicate with the subarachnoid space. Mostly, the border lines of contusion necroses are remarkably straight throughout all phases of the tissue process.

The sequence of morphologic changes with increasing survival time is described for contusion hemorrhages, as well as for necroses.

The contusion hemorrhages are differentiated from small hypertensive hemorrhages, hemorrhages in vascular softenings, and

those in local pressure necroses. The differential diagnosis of contusion necroses is discussed in regard to vascular necroses of various types.

The contusion hemorrhages, as well as necroses, result directly from pressure and shearing forces transmitted to the brain by the impact. Pathologic findings suggest that it is the initial positive-pressure phase of the compression wave caused by the impact which is mainly responsible for the development of contusion necroses.

Department of Mental Hygiene Central Anatomic Laboratory, 700 Fleet St. (2).

REFERENCES

1. Ricker, G.: Die pathologische Anatomie der frischen mechanischen Kriegsschädigungen des Hirnes und seiner Hüllen, in Handbuch der ärztlichen Erfahrungen im Weltkrieg, edited by Otto von Schjerning, Leipzig, J. A. Barth, 1921, Vol. 8, p. 334.

2. Benda, C.: Ältere Stadien von Hirn- und Rückenmarksverletzungen, in Handbuch der ärztlichen Erfahrungen im Weltkrieg, edited by Otto von Schjerning, Leipzig, J. A. Barth, 1921, Vol. 8, p. 404.

3. Spatz, H.: Kann man alte Rindendefekte traumatischer und arteriosklerotischer Genese voneinander unterscheiden? Die Bedeutung des État vermoulu, Arch. Psychiat. 90:885, 1930.

4. Spatz, H.: Über Entstehung und Bedeutung traumatischer Rindendefekte, Allg. Ztschr. Psychiat. 94:218, 1931.

5. Spatz, H.: Pathologische Anatomie der gedeckten Hirnverletzungen mit besonderer Berücksichtigung der Rindenkontusion, Arch. Psychiat. 105: 80, 1936.

6. Spatz, H.: Brain Trauma in Aviation, in German Aviation Medicine in World War II, prepared under the auspices of Surgeon General U. S. Air Force, Department of the Air Force, 1950.

7. Spatz, H., and Peters, G.: Die Rindenprellungsherde bei stumpfer Schädelverletzung, ihre Entwicklung und ihre differentialdiagnostische Bedeutung, in preparation.

8. Peters, G.: Über gedeckte Gehirnverletzungen (Rindenkontusionen) im Tierversuch, Zentralbl. Neurochir. 8:172, 1943.

9. Welte, E.: Über die Zusammenhänge zwischen anatomischem Befund und klinischem Bild bei Rindenprellungsherden nach stumpfem Schädeltrauma, Arch. Psychiat. 118:243, 1948.

10. Marie, P.: État vermoulu du cerveau, Rev. neurol. 13:1229, 1905.

11. Dougherty, M.: Sur l'état vermoulu du l'écorce cérébrale, Rev. neurol. 12:1239, 1904.

12. Klarfeld, B.: Die Anatomie der Psychosen, München, J. F. Bergmann, 1924.

13. Kodama, M.: Die regionäre Verteilung der arteriosklerotischen Veränderungen im Grosshirn, Ztschr. ges. Neurol. u. Psychiat. 102:597, 1926.

14. Hassin, G. B.: General Pathological Considerations in Brain Injury, in Injuries of Skull, Brain and Spinal Cord, Ed. 2, edited by Samuel Brock, Williams & Wilkins Company, 1943, Chap. 2.

15. Hassin, G. B.: Histopathology of the Peripheral and Central Nervous System, Ed. 3, Chicago, The Author, 1948.

16. Mittelbach, H., and Spatz, H.: Über eine eigenartige Spaltenbildung der Grosshirnwindungen ("Schizogyrie"), Zentralbl. ges. Neurol. u. Psychiat. 47:700, 1927.

17. Riederer von Paar, V.: Ein neuer Beitrag zur Frage der Schizogyrie (Windungsspaltbildung) und ihrer traumatischen Entstehung, Arch. Psychiat. 106:71, 1936.

18. Rand, C. W., and Courville, C. B.: Histologic Changes in the Brain in Cases of Fatal Injury to the Head: III. Reaction of Microglia and Oligodendroglia, Arch. Neurol. & Psychiat. 27:605, 1932.

19. Rand, C. W., and Courville, C. B.: Histologic Studies of the Brain in Cases of Fatal Injury to the Head: IV. Reaction of the Classic Neuroglia, Arch. Neurol. & Psychiat. 27:1342, 1932.

20. Rand, C. W., and Courville, C. B.: Histologic Changes in the Brain in Cases of Fatal Injury to the Head: V. Changes in the Nerve Fibers, Arch. Neurol. & Psychiat. 31:527, 1934.

21. Rand, C. W., and Courville, C. B.: Histologic Studies of the Brain in Cases of Fatal Injury to the Head: VI. Cyto-Architectonic Alterations, Arch. Neurol. & Psychiat. 36:1277, 1936.

22. Rand, C. W., and Courville, C. B.: Iron Encrustation of Nerve Cells in the Vicinity of Old Traumatic Lesions of the Cerebral Cortex, Bull. Los Angeles Neurol. Soc. 10:95, 1945.

23. Rand, C. W., and Courville, C. B.: Histologic Changes in the Brain in Cases of Fatal Injury to the Head: VII. Alterations in Nerve Cells, Arch. Neurol. & Psychiat. 55:79, 1946.

24. Rand, C. W., and Courville, C. B.: Multinucleation of Cortical Nerve Cells at the Margins of Traumatic Lesions of the Human Brain, J. Neuropath. & Exper. Neurol. 6:1, 1947.

25. Peters, G.: Die gedeckten Gehirn- und Rückenmarksverletzungen, in Handbuch der speziellen pathologischen Anatomie und Histologie: XIII. Erkrankungen des zentralen Nervensystems III, edited by F. Henke and O. Lubarsch, Berlin, Springer-Verlag, 1955, p. 84.

26. Krauland, W.: Über Hirnschäden durch stumpfe Gewalt, Deutsche Ztschr. Nervenh. 163: 265, 1949.

27. Scheinker, I. M., and Evans, J. P.: Histologic Studies of the Brain Following Head Trauma: V. Alterations in the Vessels of the Central Nervous System Following Trauma, in Trauma of the Central Nervous System A. Res. Nerv. & Ment. Dis., Proc. (1943) 24:98, 1945.

28. Evans, J. P., and Scheinker, I. M.: Histologic Studies of the Brain Following Head Trauma: VI. Post-Traumatic Central Nervous System Changes Interpreted in Terms of Circulatory Disturbances, in Trauma of the Central Nervous System, A. Res. Nerv. & Ment. Dis., Proc. (1943) 24:254, 1945.

29. Lindenberg, R.: On Morphotropic and Morphostatic Necrobiosis: Investigations on Nerve Cells of the Brain, Am. J. Path., to be published.

30. Esser, A.: Klinisches und pathologisches zur Frage des sogenannten État vermoulu, Arch. Psychiat. 93:639, 1931.

31. Anders, H. E., and Eicke, W. J.: Die Gehirngefässe beim Hochdruck, Arch. Psychiat. 112:1, 1940.

32. Lindenberg, R.: Compression of Brain Arteries as Pathogenetic Factor for Tissue Necroses and Their Areas of Predilection, J. Neuropath. & Exper. Neurol. 14:223, 1955.

33. Lindenberg, R.: Über die Anatomie der cerebralen Form der Thromboendangiitis obliterans (v. Winiwarter-Buerger), Ztschr. ges. Neurol. u. Psychiat. 167:554, 1939.

34. Lindenberg, R., and Spatz, H.: Über die Thromboendarteriitis obliterans der Hirngefässe (cerebrale Form der V. Winiwarter-Buergerschen Krankheit), Arch. path. Anat. 305:531, 1939.

35. Lynn, J. G., and Putnam, T. J.: Histology of Cerebral Lesions Produced by Focused Ultrasound, Am. J. Path. 20:637, 1944.

36. Peters, G.: Schädigungen des Zentralnervensystems durch Ultraschall, in Handbuch der speziellen pathologischen Anatomie und Histologie: XIII. Erkrankungen des zentralen Nervensystems, III, edited by F. Henke and O. Lubarsch, Berlin, Springer-Verlag, 1955, p. 363.

37. Balthasar, K. G.: Histology of Aimed Hypothermal Brain Injuries in Cats, J. Neuropath. & Exper. Neurol. 15:211, 1956.

38. Ricker, G., and Döring, G.: Commotio cerebri, in Handbuch der speziellen pathologischen Anatomie und Histologie: XIII. Erkrankungen des zentralen Nervensystems, III, edited by F. Henke and O. Lubarsch, Berlin, Springer-Verlag, 1955, p. 177.

39. Hallervorden, J.: Hirnerschütterung und Thixotropie, Zentralbl. Neurochir. 6:37, 1941.

40. Gurdjian, E. S.; Lissner, H. R.; Latimer, F. R.; Haddad, B. F., and Webster, J. E.: Quantitative Determination of Acceleration and Intracranial Pressure in Experimental Head Injury: Preliminary Report, Neurology 3:417, 1953.

41. Coe, G. B.; MacNamee, J. K., and Herget, C. M.: Brain Injury from Local Impact Without Skull Fracture, Mil. Surgeon 111:428, 1952.

42. Gurdjian, E. S.; Webster, J. E., and Lissner, H. R.: Observations on the Mechanism of Brain Concussion, Contusion and Laceration, Surg. Gynec. & Obst. 101:680, 1955.

43. Sjövall, H.: The Genesis of Skull and Brain Injuries, Acta path. et microbiol. scandinav., Supp. 48, 1943.

Survival of Rats with Induced Congenital Cardiovascular Anomalies

The Use of Trypan Blue as a Practical Experimental Approach to Production of Congenital Cardiovascular Anomalies in Rats Capable of Long Postnatal Survival

SIDNEY M. RICHMAN, A.B.; WILBUR A. THOMAS, M.D., and NADYA KONIKOV, M.D., St. Louis

One of the most useful approaches to the study of any disease is to reproduce it in experimental animals. Cardiovascular anomalies have been produced in the fetuses of rats and other animals by various means, including subjecting the mother at a critical period to irradiation,[1,2] folic acid deficiency,[3,4] folic acid antagonists,[5] vitamin A deficiency,[6,7] vitamin E deficiency,[8] and anoxia.[9,10] However, the fetuses with cardiovascular anomalies have either died or been killed in utero or at birth. We are unaware of any reports of the long postnatal survival of groups of animals with induced cardiovascular anomalies.

Fox and Goss[11] recently reported the production of cardiovascular anomalies in a high percentage of rat fetuses by injecting trypan blue into pregnant female rats. All of the fetuses were killed in utero, and no information was obtained regarding their ability to survive postnatally. Since Fox and Goss reported that the anomalies in their rats were often limited to the cardiovascular system, we thought it possible that such animals might survive after birth. Hence, we have designed an experiment to determine whether or not rats with congenital cardiovascular anomalies produced by the method used by Fox and Goss would survive beyond birth. The results have far exceeded our expectations. Fifty surviving rats whose mothers had been injected with trypan blue during pregnancy were killed 22 to 33 days after birth, and twenty-six of them had major cardiovascular anomalies.

The purpose of this report is to present an account of the methods we have used and the types of anomalies that were obtained.

Materials and Methods

Thirty female rats of the Wistar strain were obtained from the Charles River Breeding Laboratory, in Boston. They were given Purina Rat Chow and water ad libitum. Vaginal smears were taken daily in order to determine the phase of the ovulatory cycle. The smears were examined by phase microscopy; however, an ordinary light microscope with either stained or unstained smears will suffice if phase contrast methods are not available. The female rats were placed with males in a ratio of 4:1 at the appropriate time of the estrus cycle.[12] Smears were taken the following morning and examined for the presence of sperm, and the presence of sperm invariably indicated impregnation. If spermatozoa were present, the time of insemination was arbitrarily dated 12:00 p.m. in order to standardize the procedure. The impregnated rats were then isolated in separate cages provided with nesting areas for the young. Eight and one-half days following insemination 1 ml. of a 1% aqueous solution of trypan blue * was injected subcutaneously into the pregnant rats. All of the mothers carried their fetuses for the normal gestation time (approximately 21 days after insemination) and gave birth spontaneously.

Submitted for publication Aug. 16, 1956.

A junior year medical student and a Josiah Macy, Jr. Research Fellow at the time this work was done (Mr. Richman). Assistant Professor of Pathology (Dr. Thomas). Instructor in Pathology (Dr. Konikov).

From the Department of Pathology, Washington University School of Medicine. This study was supported by Grant H-1820 from the National Heart Institute, Institutes of Health, U. S. Public Health Service, Bethesda, Md.

* Prepared by the Allied Chemical and Dye Corporation of New York.

The rats that were born dead or that died within a short time after birth were fixed in 10% formalin, and the surviving rats were allowed to remain with their mothers for 21 days, after which they were weaned. These offspring were then placed in group cages (but with each litter identified), where they remained until they were killed. They were given the same diet given their mothers and water ad libitum.

The total new population was 216 baby rats. Using the random sampling technique, 50 of these rats were selected to be killed approximately 30 days after birth. These rats were killed by the inhalation of ether and were dissected under 5 × magnification immediately after death.

Our main attention was focused on the cardiovascular system; the heart and lungs were left together in order to demonstrate clearly the major vessels. In addition, all external abnormalities were recorded, and the contents of the peritoneal cavity were examined. However, no attempt was made to determine minute anomalies outside the cardiovascular system.

Results

The 30 pregnant rats gave birth to 216 offspring. Twenty-five (25) were born dead or died within two days after birth. At the age of killing, 191 were still alive. Fifty of these were selected at random and killed 22 to 33 days after birth. This report is primarily concerned with these 50 animals.

The anomalies found in these 50 rats are recorded in Tables 1 to 3. Of the 50 rats, 11 had external abnormalities, such as malformations of the extremities or hydrocephalus (Figs. 4, 5); 3 of these 11 also had cardiovascular anomalies.

TABLE 1.—*Trypan-Blue-Induced Anomalies Among Fifty Rats That Were Killed Twenty-Two to Thirty-Three Days After Birth*

Rat No.	Age, Days	Sex	Cardiovascular Anomalies*	Other Anomalies
1	22	F	Normal	
2	22	M	Abnormal aortic arch; distally arising right subclavian	
3	23	M	Normal	
4	23	M	Normal	
5	23	M	IV septal defect	
6	25	M	IV septal defect; IA septal defect	
7	25	M	Overriding aorta; atretic PA, patent DA; IA septal defect	
8	25	M	Normal	Bilateral clubfoot
9	25	F	IV septal defect	
10	25	F	Normal	Bilateral clubfoot
11	25	F	Normal	Hydrocephalus
12	27	F	IV septal defect; patent DA; stenosis of PA	
13	27	F	IV septal defect	Bilateral clubfoot
14	27	F	Rudimentary right atrium; IA septal defect	
15	27	M	Normal	
16	27	F	Normal	Hydrocephalus
17	27	F	Normal	
18	27	M	IV septal defect	Hydrocephalus
19	28	M	IV septal defect	
20	28	M	Rudimentary right atrium; IV septal defect	
21	28	M	Normal	Hydrocephalus
22	28	M	Absence of right atrium	
23	28	F	Normal	
24	29	M	Normal	
25	29	F	IV septal defect	
26	29	F	IA septal defect	
27	29	F	IV septal defect	
28	29	M	Normal	
29	29	F	IA septal defect	
30	30	F	IV septal defect	
31	30	M	Both atria on right side; patent DA; High IV septal defect; stenosis of PA	
32	30	F	Normal	Hydrocephalus
33	30	M	Normal	
34	31	M	Normal	
35	31	M	Normal	
36	31	M	IV septal defect	
37	32	M	IV septal defect	
38	32	M	Absence of IV septum	
39	32	?	Normal	
40	32	M	Normal	
41	32	F	Normal	
42	32	F	Absence of IV septum; overriding aorta; patent DA	
43	32	F	Normal	Hydrocephalus
44	32	M	IA septal defect	
45	32	F	Normal	
46	33	M	Patent DA	Hydrocephalus
47	33	M	IV septal defect	
48	33	F	Normal	Situs inversus
49	33	M	IA septal defect	
50	33	F	Normal	

*IV indicates interventricular; IA, interatrial; DA, ductus arteriosus; PA, pulmonary artery.

TABLE 2.—*Summary of Common Types of Cardiovascular Anomalies* Observed Among Fifty Rats Listed in Table 1*

Type of Cardiovascular Lesion	No. of Rats	Incidence	
		Percentage of Total CV Lesions	Percentage of Total 50 Rats
IV septal defect	17	65	34
IA septal defect	7	27	14
Patent DA	5	19	10
Stenosis or atresia of pulmonary outlet	3	11	6

*This classification includes lesions existing either alone or in a complex.

TABLE 3.—*Summary of Incidence of Anomalies Among the Fifty Rats Listed in Table 1*

	No. of Rats	Percentage of Total
A Normal animals	16	32%
B Cardiovascular lesions only	23	46%
C Cardiovascular lesions and other anomalies	3	6%
D Other anomalies only	8	16%
E Total cardiovascular lesions in both (B) & (C)	26	52%
F Total other anomalies in both (C) & (D)	11	22%

The remaining 39 of the 50 rats had no external abnormalities and during life appeared to be healthy, normal rats. They all grew and gained weight at approximately the same rate (Fig. 6). A typical rat in this group weighed 85 gm. at the end of one month. However, when these animals were killed and autopsied, we found major cardiovascular anomalies in 23 (Tables 1, 2, 3). The commonest and most striking cardiovascular anomaly was the interventricular septal defect, and this type of defect was found more frequently in the muscular septum than in the membranous septum (Figs. 1, 2). Occasionally the entire interventricular septum was absent. The hearts were left attached to the lungs after dissection in order to demonstrate the relation of the great vessels more clearly and were fixed in formalin. Therefore, accurate weights of the hearts could not be obtained. However, as demonstrated in Figure 3, some of the hearts with large interventricular septal defects were greatly enlarged. None of the animals had any evidence of congestive failure during life or at the time of autopsy.

Comment

The production of cardiovascular anomalies in animals that can survive postnatally should provide a useful new approach to the study of congenital heart disease. It is the purpose of this paper to present a method of inducing these anomalies which we feel will be a powerful tool in investigating many physiological and anatomical problems related to congenital heart disease.

From our own particular standpoint, we have been especially interested in the study of the development of pulmonary arterial lesions in human patients with cardiovascular anomalies.[13] Many of our conclusions, which were of necessity based on indirect observations in human autopsy material, can now be tested more directly in experimental animals. This type of approach should be applicable likewise to many other problems.

It is rather interesting to note that none of the animals showed evidence of congestive heart failure in spite of the presence of major anomalies. We intend to observe the remaining survivors of this experiment for a much longer period of time and to subject some of these animals to various stressful situations, including prolonged exercise, in an attempt to produce congestive failure.

Of particular value in experiments that require observations of the living animal is that the control group is included with the experimental and that it is impossible to distinguish between the two groups until the final autopsies are performed. The rats without external anomalies but with congenital cardiovascular lesions looked and acted similarly to the normal rats, giving no evidence of disease until killed.

Fig. 1.—Large interventricular septal defect in a one-month-old rat. Each small unit on the scale in this and in the subsequent Figures represents 1 mm.

Fig. 2.—Small interventricular defect in the muscular septum of a one-month-old rat.

Fig. 3.—Enlarged heart occupying most of the open thoracic cage of a one-month-old rat. This heart was subsequently dissected and found to have a large interventricular septal defect.

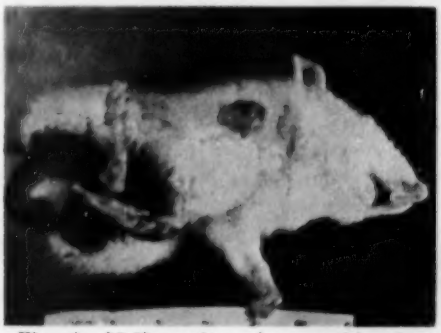


Fig. 4.—Malformation of extremities in a one-month-old rat.

Fig. 5.—A one-month-old rat with hydrocephalus.

Fig. 6.—Photograph demonstrating rate of growth. Shown are a full-term fetus and a 22-day-old rat from the same littter. The larger rat weighed 55 gm. and was subsequently found to have a congenital cardiovascular defect.

Trypan blue has been known to produce skeletal and neurological defects in the fetuses of mice and rats for some time.[5,14, 15-22] However, no investigators had focused their attention especially on the effect the dye had on the cardiovascular system until the recent work of Fox and Goss.[11] Of the diazo dyes tested for teratogenic properties by Wilson, only trypan blue gave a high yield of cardiovascular anomalies; it alone was accumulated in the reticuloendothelial system and the renal tubules of the mother.[22] In the adult rat, the repeated administration of the dye results in anemia, increase in the erythrocyte sedimentation rate, fatty change of the liver, hyalinization of the renal glomeruli, and hyperplasia of the lymph nodes, spleen, and adrenals.[14]

The mode of action of trypan blue upon the fetus is not known. Among those mechanisms suggested have been direct action on the fetus, action at the placental level to interfere with exchanges, and an indirect effect secondary to changes brought about in maternal physiology. The dye has not been shown to cross the placenta. It has not been demonstrated in the tissues of either the placenta or the fetus.[22] The incidence of skeletal and cranial anomalies is greater in fetuses of mothers who received the dye prior to as well as during pregnancy.[15]

The administration of the dye at the seventh to the ninth day of gestation in the rat appears to give rise to the highest yield of anomalies. It is entirely possible that the effect of the dye does not reach its height for some time after administration.

While deficiency of folic acid produces cardiovascular defects in fetal rats, they are predominantly of the aortic arch, as opposed to the higher number of cardiac defects obtained by use of trypan blue.[3,11] The chemistry of trypan blue does not suggest that it is a metabolic antagonist to any of the vitamins.

Embryological changes observed in fetuses of mice treated with trypan blue consisted mainly of edema at the head region, swelling of the pericardial sac, and enlargement of the heart.[18,19] Detailed examination of the cardiovascular systems was not reported.

We found, as have others, that there is great variation in the sensitivity of the fetus to the effect of trypan blue. The presence of anomalies among litter mates appeared to be entirely random.

Summary

A practical method is presented for the production of congenital cardiovascular amonalies in rats that are capable of surviving for at least one month after birth.

Thirty pregnant rats were injected subcutaneously with trypan blue eight and one-half days after insemination. These rats gave birth to 216 young rats, and 191 of these survived for 22 days or more after birth. Fifty of these 191 were killed at 22 to 33 days of age. Of these 50 rats, 26 had major cardiovascular anomalies. Interventricular septal defects were present in 17 and represented the commonest single malformation.

We are unaware of any previous reports of a similar long postnatal survival of groups of animals with induced cardiovascular anomalies.

Washington University School of Medicine (Dr. Thomas).

REFERENCES

1. Wilson, J. G., and Karr, V. W.: Effects of Irradiation on Embryonic Development: I. X-Rays on the 10th Day of Gestation in the Rat, Am. J. Anat. 88:1, 1951.

2. Jordan, H. C., and Brent, R. L.: Effects of Irradiation on Embryonic Development: II. X-Rays on the 9th Day of Gestation in the Rat, Am. J. Anat. 92:153, 1953.

3. Baird, C. D.; Nelson, M. M.; Monie, I. W., and Evans, H. M.: Congenital Cardiovascular Anomalies Induced by Maternal Pteroylglutamic Acid Deficiency During Gestation in the Rat, Circulation Res. 2:544, 1954.

4. Nelson, M. M.; Asling, C. W., and Evans, H. M.: Production of Multiple Congenital Abnormalities in Young by Maternal Pteroylglutamic Acid Deficiency During Gestation, J. Nutrition 48:61, 1952.

5. Hogan, A. G.; O'Dell, B. L., and Whitley, J. R.: Maternal Nutrition and Hydrocephalus in Newborn Rats, Proc. Soc. Exper. Biol. & Med. 74:293, 1950.

6. Wilson, J. G.; Roth, C. B., and Warkany, J.: An Analysis of the Syndrome of Malformations Induced by Maternal Vitamin A Deficiency: Effects of Restoration of Vitamin A at Various Times During Gestation, Am. J. Anat. 92:189, 1953.

7. Wilson, J. G., and Warkany, J.: Aortic-Arch and Cardiac Anomalies in the Offspring of Vitamin A Deficient Rats, Am. J. Anat. 85: 113, 1949.

8. Cheng, D. W., and Thomas, B. H.: Relationship of Time of Therapy to Teratogeny in Maternal Avitaminosis E, Proc. Iowa Acad. Sc. 60:290, 1953.

9. Ingalls, T. H.; Curley, F. J., and Prindle, R. A.: Anoxia as a Cause of Fetal Death and Congenital Defects in the Mouse, Am. J. Dis. Child. 80:34, 1950.

10. Ingalls, T. H.; Curley, F. J., and Prindle, R. A.: Experimental Production of Congenital Anomalies: Timing and Degree of Anoxia as Factors Causing Fetal Deaths and Congenital Anomalies in the Mouse, New England J. Med. 247:758, 1952.

11. Fox, M. H., and Goss, C. M.: Experimental Production of a Syndrome of Congenital Cardiovascular Defects in Rats, Anat. Rec. 124: 189, 1956.

12. Farris, E. J., and Griffith, J. Q.: The Rat in Laboratory Investigation, Second Edition, Philadelphia, J. B. Lippincott Company, 1949.

13. O'Neal, R. M., and Thomas, W. A.: Role of Pulmonary Hypertension and Thromboembolism in the Production of Pulmonary Arteriosclerosis, Circulation 12:370, 1955.

14. Gillman, J.; Gilbert, C.; Gillman, T., and Spence, I.: A Preliminary Report on Hydrocephalus, Spina Bifida and Other Congenital Anomalies in the Rat Produced by Trypan Blue: Significance of These Results in the Interpretation of Congenital Anomalies Following Maternal Rubella, South African J. M. Sc. 13: 47, 1948.

15. Gillman, J.; Gilbert, C.; Spence, I., and Gillman, T.: A Further Report on Congenital Anomalies in the Rat Produced by Trypan Blue, South African J. M. Sc. 16:125, 1951.

16. Hamburgh, M.: Malformations in Mouse Embryos Induced by Trypan Blue, Nature 169: 27, 1952.

17. Hamburgh, M.: The Embryology of Trypan Blue Induced Abnormalities in Mice, Anat. Rec. 119:409, 1954.

18. Waddington, C. H., and Carter, T. C.: Malformations in Mouse Embryos Induced by Trypan Blue, Nature 169:27, 1952.

19. Waddington, C. H., and Carter, T. C.: A Note on Abnormalities Induced in Mouse Embryos by Trypan Blue, J. Embryol. & Exper. Morphol. 1:167, 1953.

20. Wilson, J. G.: Congenital Malformation Produced by Injecting Azo Blue into Pregnant Rats, Proc. Soc. Exper. Biol. & Med. 85:319, 1954.

21. Wilson, J. G.: Withdrawal of Claim That Azo Blue Causes Congenital Malformations, Proc. Soc. Exper. Biol. & Med. 87:1, 1954.

22. Wilson, J. G.: Teratogenic Activity of Several Azo Dyes Chemically Related to Azo Blue, Anat. Rec. 123:313, 1955.

Nonlipid Reticuloendotheliosis in an Adult

Report of a Case

CAPT. DALE M. SCHULZ (MC), U.S.A. (Res.); MAJOR GEORGE B. HAMILTON (MC), U.S.A., and LIEUT. LESTON B. NAY (MC), U.S.A.

In recent years nonlipid reticuloendotheliosis (Letterer-Siwe disease) has been recognized with increasing frequency in infants and young children. Despite this renewed interest in the condition, very few cases in adults have been reported. In 1939 Scott and Robb-Smith[1] described an entity which they termed histiocytic medullary reticulosis in four adult patients. They felt that the clinical course and pathologic findings corresponded to those of Letterer-Siwe disease in children. Several additional cases have been reported more recently under the same name, some of which were considered by the authors to be "atypical."[2-4] Two men with systemic reticuloendotheliosis have been reported by Paull and Phillips[5] as cases of Letterer-Siwe disease. The case of Dennis and Rosahn,[6] described in 1951, appears to conform most closely to the criteria usually imposed for the diagnosis of Letterer-Siwe disease. Lichtenstein,[7] writing in 1953, mentioned that he had seen three similar cases in adults.

Report of Case

The patient, a 57-year-old white man, was admitted to Valley Forge Army Hospital in January, 1956, because of progressive weakness, weight loss, and ascites. His relevant medical history began in 1945, when he was forced to wear a body cast for almost a year for a compression fracture of a thoracic vertebra. Upon removal of this cast an erythematous, maculopapular rash was discovered across the shoulders and posterior thorax. This gradually spread to the anterior chest and all four extremities. Biopsies of the skin at that time and again in 1952 failed to yield a definite diagnosis.

Abdominal discomfort was first experienced in 1950, at which time a duodenal ulcer was demonstrated roentgenologically. He responded to medical management, but right upper quadrant pain led to a cholecystectomy the following year. In 1953 he began to notice weakness, lassitude, and weight loss, which continued until September, 1955, when a gradual increase in girth was noted. He was hospitalized, and physical examination on admission showed ascites, an enlarged liver, which was felt 4 cm. below the costal margin, and generalized enlargement of lymph nodes. Three thousand milliliters of blood-tinged fluid was removed by thoracentesis.

After transfer to a second hospital, 3220 ml. of additional fluid was removed. A diagnosis of cirrhosis was made on the basis of a punch biopsy of the liver. Significant laboratory data included a peripheral eosinophilia of 10%, a sedimentation rate of 26 mm. per hour, thymol turbidity of 10 units, sulfobromophthalein (Bromsulphalein) retention of 12%, and a serum alkaline phosphatase of 20 S.J.R. units.* Total serum proteins were 6.2 gm. per 100 ml., with an albumin-globulin ratio of 2.0/4.2. Exploratory laparotomy was performed in November, 1955. The peritoneal cavity contained 2500 ml. of clear fluid. The liver was enlarged, firm, and coarsely nodular. The spleen was enlarged to a less degree, and the capsule was thickened and hyalinized. Generalized enlargement of the mesenteric lymph nodes was noted. Biopsy specimens were taken from the liver, spleen, and nodes. Two weeks later the patient began to have gross melena and hematemesis and was reexplored. A penetrating posterior duodenal ulcer was found, and a partial gastrectomy was performed. He did well postoperatively and was transferred to Valley Forge Army Hospital.

On admission to this hospital he was emaciated and appeared chronically ill. The rash, which had appeared some 10 years previously, was still present

Submitted for publication Aug. 8, 1956.

From the Pathology Service and the Department of Medicine, Valley Forge Army Hospital, Phoenixville, Pa.

*Shinowara-Jones-Reinhart units; normal 2-9 units.

on the chest and back and to a less extent on the arms and legs. It consisted of discrete maculopapules 2-4 mm. in diameter, as well as larger confluent areas. The lesions blanched on pressure, but some hyperpigmentation remained. Venous distention was noted over the abdomen. The liver edge was down 6 cm., and a fluid wave could be felt in the abdomen. The spleen was not demonstrated.

Initial blood counts showed a leukocytosis of approximately 13,000 with 10% to 15% eosinophils. Total eosinophil counts ranged from 1385 to 1600 per cubic millimeter. Administration of corticotropin caused a drop of 50% in two hours and of 90% in eight hours. Hemoglobin was 13 gm. per 100 cc., with an hematocrit of 30%. Sedimentation rate was 35 mm. per hour. A bone-marrow aspirate from the sternum showed no abnormalities except an eosinophil count of 17%, including 2% of eosinophilic myelocytes. Liver function tests included "4 plus" cephalin flocculation, thymol turbidity of 8.4 units, and an alkaline phosphatase level of 6.7 S.J.R. units. Total serum protein was 7.2 gm. per 100 ml., with an albumin-globulin ratio of 2.7/4.5. The fasting blood sugar was 90 mg. per 100 ml. An oral glucose tolerance test gave values (expressed as milligrams per 100 ml.) of 232, 274, 197, and 83 at one-half, one, two, and three hours, respectively. Other laboratory data, including serum calcium and phosphorus, total cholesterol, nonprotein nitrogen, and phenolsulfonphthalein excretion, were within normal limits.

The lung fields were normal on roentgenographic examination, and no evidence of ulceration was found in the alimentary tract. A roentgenographic bone survey revealed widespread, spotty demineralization of bones with finely trabeculated cystic areas, especially in the pelvis, ribs, upper extremities, and heads of the clavicles. There were no focal areas of decreased density in the skull.

The patient was placed on a high-vitamin, high-calorie diet combined with the use of intravenous salt-free albumin. There were a progressive decrease in ascites and a gradual return of liver function to near-normal levels. In May, 1956, after five months of hospitalization, sulfobromophthalein retention was 4%, thymol turbidity 5.8 units, and alkaline phosphatase 1.9 S.J.R. units. The serum proteins increased to 8.9 gm. per 100 ml. with an albumin-globulin ratio of 4.6/4.3. Early in the course of this hospitalization biopsy specimens were taken from the skin of the back and from a rib. He was discharged from the hospital in June, 1956, symptomatically improved.

Examination of Tissues

Duodenum.—A description of the gross appearance of the duodenal ulcer removed at the second laparotomy is not available. Microscopically, the ulcer base was covered by a thin layer of fibrin and vascular granulation tissue. The submucosa adjacent to the defect was widened and replaced by rather dense fibrous tissue. The muscle underlying the ulcer base was also fibrotic. The collagen bands of the submucosa were separated by linear deposits of lymphocytes, histiocytes, a few plasma

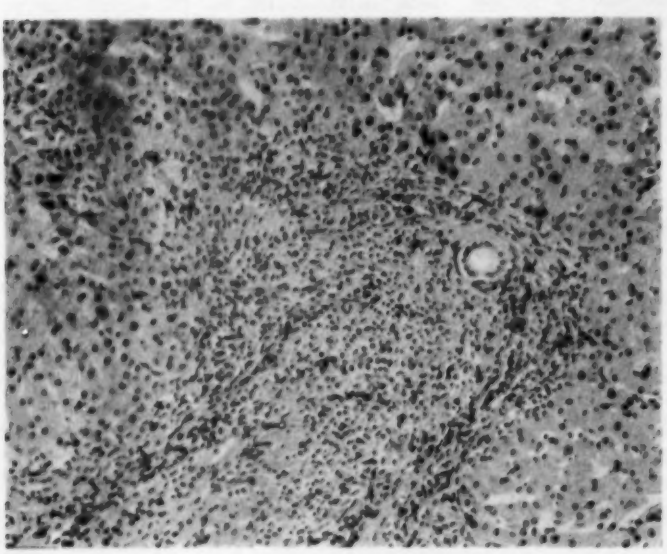


Fig. 1.—Liver. The portal area is widened by histiocytes arranged in poorly defined whorls. There is no increase in fibrous tissue. Reduced to 92% of mag. × 110.

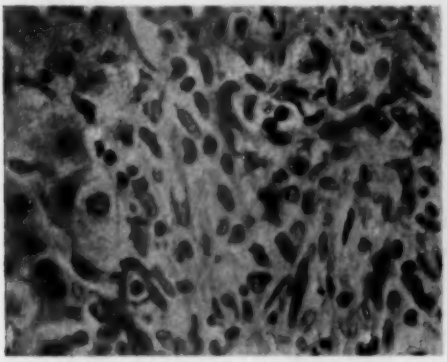


Fig. 2.—Liver. The edge of a portal area infiltrated by histiocytes, lymphocytes, and eosinophils. The hepatic cells show variation in nuclear size and staining. Reduced to 61.5% of mag. × 590.

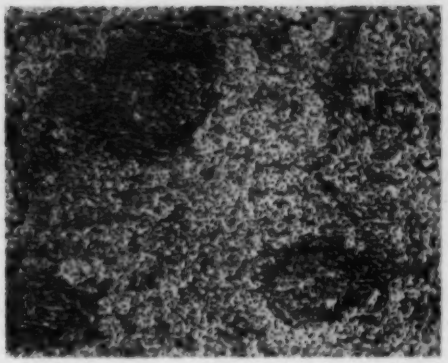


Fig. 3.—Mesenteric lymph node. The small follicles are widely separated by sheets of histiocytes, mixed with eosinophils and lymphocytes. Reduced to 61.5% of mag. × 110.

cells, and many eosinophils. In some areas the histiocyte was the predominating cell type. The eosinophils were unevenly distributed.

Liver.—The normal lobular pattern was disrupted by an increase in size and cellularity of the portal areas. The infiltrating cells were arranged in poorly defined whorls in some areas. In some foci the hepatic cells were replaced by whorled masses of cells which were not obviously associated with a portal space. The individual cells were for the most part histiocytes, characterized by indented, pale, finely granular nuclei. There were a few lymphocytes and varying numbers of eosinophils. Despite the increased area of the portal spaces, no increase in collagen could be demonstrated by differential stains. There was not an increase in the number of bile passages, nor was there evidence of bile stasis. The liver cord cells were disarranged, and the nuclei varied greatly in size and intensity of staining. A number of the hepatic cells were binucleated. None contained fat vacuoles. The Kupffer cells were not unusually prominent.

Lymph Nodes.—Two of four sections of lymph node showed decrease in the size of the follicles and marked sinusoidal hyperplasia. In the other two sections the changes were more striking. Only a few small follicles remained, which were separated widely by whorled masses of large pale cells. Most of these cells had poorly defined cytoplasmic boundaries and lightly staining, irregularly ovoid or indented nuclei with finely divided chromatin and inconspicuous nucleoli. These cells were considered to be histiocytes. There were also some reticulum cells, scattered lymphocytes, and a moderate number of eosinophils. As in the other tissues, the eosinophils were unevenly distributed.

Spleen.—The thickened capsule was composed of dense, relatively acellular, partially hyalinized fibrous tissue. No lymphoid follicles were seen. The sinusoids were open but empty. The intersinusoidal tissue consisted of a loose, lacy fibrous network, sparsely sprinkled with lymphocytes, histiocytes, and rare eosinophils. Some of the thickened trabeculae were deeply stained by blue-green iron pigment. Small deposits of hemosiderin were present also.

Skin.—Other than an increased amount of pigment in the basal layer, the epidermis showed no changes. The upper dermis contained a patchy cellular infiltrate. Some of the cells were histiocytes, while others had darker nuclei and prominent, granular cytoplasm. Staining by the Dominici technique demonstrated fine blue granules in the cytoplasm, identifying the cells as mast cells. These and the histiocytes were present in approximately equal numbers. There was

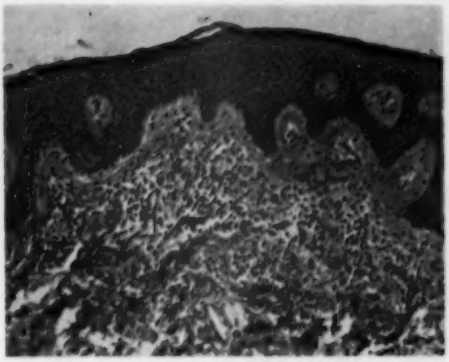


Fig. 4.—Skin. The dermis contains a patchy infiltrate consisting of histiocytes and mast cells together with scattered lymphocytes. Reduced to 61.5% of mag. × 110.

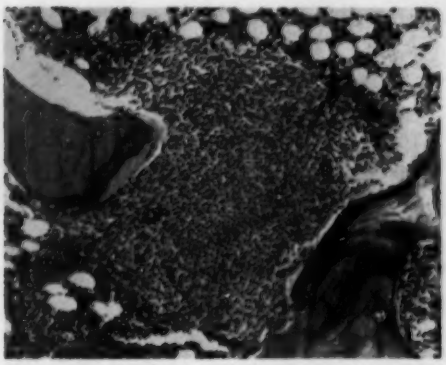


Fig. 5.—Rib. A nodule of histiocytes infiltrated by eosinophils partially replaces the marrow. Reduced to 61.5% of mag. × 110.

a slight lymphocytic infiltrate about the somewhat dilated capillaries and the skin appendages. No eosinophils were seen.

Rib.—A 2 cm. section of the left fifth rib was examined. No focal lesions could be seen grossly on the cut surfaces. Microscopically, approximately one-half of the total area of the marrow spaces was occupied by well-defined nodules, composed almost entirely of histiocytes. These cells were closely packed together in sheets with a few scattered lymphocytes. The nodules were moderately to heavily infiltrated by unevenly distributed eosinophils. Many of the bony trabeculae adjacent to these nodules showed mild erosion. A few trabeculae also showed slight evidence of new bone formation. The uninvolved marrow was approximately 50% cellular, with the various elements present in the usual proportions except for a slight increase in the number of eosinophils.

Comment

Discussions of the nosologic position of Letterer-Siwe disease fall into two principal groups: those in which the condition is regarded as inflammatory in origin, related to Hand-Schüller-Christian disease and eosinophilic granuloma,[7] and those in which it is considered to be related to malignant neoplasms of the reticuloendothelial system.[8-10] The now widely accepted concept that Letterer-Siwe disease, Hand-Schüller-Christian disease, and eosinophilic granuloma are different manifestations of the same entity resulted from the accumulation of reports of cases in which features of two or more of these conditions occurred in the same patient, usually a child or young person. The small number of adult cases which have been described under the general term "nonlipid reticuloendotheliosis" present an even more confusing picture. Many of the cases bear only a slight resemblance, either clinically or pathologically, to others in the group.

As originally described by Scott and Robb-Smith,[1] histiocytic medullary reticulosis in adults is characterized by a rapidly fatal clinical course, with fever, pancytopenia, petechiae and other hemorrhagic manifestations, and jaundice. The liver, spleen, and lymph nodes are enlarged. Generalized hyperplasia of the reticuloendothelial system is found microscopically. Except for bone lesions, these criteria correspond with those given by Varga, Richter, and DeSanctis[11] for the recognition of Letterer-Siwe disease in children. More recently reported cases of histiocytic medullary reticulosis have shown some variations. One of the cases of Civin, Gotshalk, and Okazaki[3] showed "fat-filled histiocytes" in the lymph nodes, and Asher[4] reported a case without enlargement of lymph nodes.

In one of the two cases described as systemic reticuloendotheliosis by Paull and Phillips[5] the lesions were confined entirely to the skeletal system. In the second case, a 30-year-old man, the diagnosis of Letterer-Siwe disease was made, even though "lipoid-laden cells" were seen in the liver and were apparently a prominent feature in the lymph nodes. The case of Dennis and Rosahn,[6] also a 30-year-old man, resembled Letterer-Siwe disease histologically more closely than most of the reported cases, although the clinical course was more like that of Hand-Schüller-Christian disease.

From the above review, it seems probable that several different entities have been described under the same or similar names. The relationship of these individual conditions and the relation between them and reticuloendotheliosis in children is obscure. The present case combines some of the features of several of the diseases seen in children. The skin lesions correspond both clinically and histologically to those of Letterer-Siwe disease. The granulomatous histiocytic proliferation and lack of foam cells in the liver, spleen, and lymph nodes also resemble this disease rather than Hand-Schüller-Christian disease, even though the prominence of eosinophils in the lymph nodes and liver suggests the latter. The widespread bone lesions are typical of eosinophilic granuloma as it occurs as an isolated entity in younger persons. There is little resemblance to histiocytic medullary reticulosis, particularly clinically. The prolonged course is unlike Letterer-Siwe disease and does not suggest a relationship to the malignant reticuloendothelioses.

The present case is unusual in several respects: (1) the age of the patient (57 years), (2) the duration of symptoms, which began over 10 years before, (3) the presence of typical eosinophilic granulomas of bone, (4) the striking eosinophilic and histiocytic infiltration about a chronic duodenal ulcer, and (5) the prominence of mast cells in the skin lesions. Although most authors have not considered that eosinophilic granulomas of the gastrointestinal tract, as described by Vanek,[12] are associated with a systemic disease, it is interesting to speculate on the possible significance of a similar lesion in this patient, particularly in view of the unusual number of histiocytes in the ulcer wall. The presence of mast cells, as well as histiocytes, in the dermis substantiates the discussion of Lynch and associates[9] on the similarities and possible relationship between the reticuloendothelioses and urticaria pigmentosa. In a fatal case of urticaria pigmentosa reported by Ellis[13] there were generalized mast-cell infiltrates in the viscera. Especially interesting is the fact that the infiltrating mast cells in this case were often associated with eosinophils, and, in some sections, with histiocytes as well.

Summary

A case of nonlipid reticuloendotheliosis occurring in a 57-year-old man is presented. The histiologic changes resemble those found in Letterer-Siwe disease in infants, but the clinical course has been prolonged, extending over a period of more than 10 years. Similar cases from the literature are discussed in relation to the present case.

Valley Forge Army Hospital, Phoenixville, Pa.

REFERENCES

1. Scott, R. B., and Robb-Smith, A. H. T.: Histiocytic Medullary Reticulosis, Lancet 2:194-198 (July 22) 1939.

2. McGovern, V. J.; Morrow, A. W., and Thomson, E. F.: A Case of Histiocytic Medullary Reticulosis, J. Path. & Bact. 63:340-343 (April) 1951.

3. Civin, H.; Gotshalk, H. C., and Okazaki, K.: Histiocytic Medullary Reticulosis, A. M. A. Arch. Int. Med. 94:375-383 (Sept.) 1954.

4. Asher, R.: Histiocytic Medullary Reticulosis: Case Without Lymphadenopathy, Lancet 1: 650-651 (May) 1946.

5. Paull, A. M., and Phillips, A. M.: Systemic Reticuloendotheliosis (Letterer-Siwe Disease) in the Adult Male, Ann. Int. Med. 41:363-371 (Aug.) 1954.

6. Dennis, J. W., and Rosahn, P. D.: The Primary Reticulo-Endothelial Granulomas, with Report of an Atypical Case of Letterer-Siwe's Disease, Am. J. Path. 27:627-653 (July-Aug.) 1951.

7. Lichtenstein, L.: Histiocytosis X: Integration of Eosinophilic Granuloma of Bone, "Letterer-Siwe Disease," and "Schüller-Christian Disease" as Related Manifestations of a Single Nosologic Entity, A. M. A. Arch. Path. 56:84-102 (July) 1953.

8. Gray, J. D., and Taylor, S.: Acute Systemic Reticulo-Endotheliosis Terminating as a Monocytic Leukæmia, Cancer 6:333-337 (March) 1953.

9. Lynch, M. J. G.; Bain, H. W.; Stanyon, J. H., and Crang, C. L.: Reticuloblastomatosis and the Letterer-Siwe Syndrome, Cancer 7:168-178 (Jan.) 1954.

10. Mermann, A. C., and Dargeon, H. W.: Management of Certain Nonlipid Reticulo-Endothelioses, Cancer 8:112-122 (Jan.) 1955.

11. Varga, C.; Richter, M. N., and DeSanctis, A. G.: Systemic Aleukemic Reticuloendotheliosis (Letterer-Siwe Disease), Am. J. Dis. Child. 75: 376-384 (March) 1948.

12. Vanek, J.: Gastric Submucosal Granuloma with Eosinophilic Infiltration, Am. J. Path. 25: 397-407 (May) 1949.

13. Ellis, J. M.: Urticaria Pigmentosa: Report of a Case with Autopsy, Arch. Path. 48:426-435 (Nov.) 1949.

Pathogenesis of Poliomyelitis in the Chick Embryo

ROBERT LOVE, M.D., and MANUEL ROCA-GARCIA, M.D., Pearl River, N. Y.

Inoculation of the yolk sac with the chick-embryo-adapted MEF_1 strain of poliomyelitis produces an infection which resembles poliomyelitis in higher animals.[1] A stage of extraneural infection, during which the greatest concentration of virus is found in the yolk sac and blood, is followed by a stage of neural infection, characterized by high virus content and pathologic changes in the nervous system.[1] The exact mode of spread from yolk sac to the nervous system has not been demonstrated. The present experiments were designed to elucidate this point by an evaluation of the distribution of lesions and of virus during the early stages of infection which follow the introduction of virus by the yolk sac and intravenous routes.

Material and Methods

Embryos.—White Leghorn embryos were used throughout.

Virus.—The inocula were prepared from the 44th egg passage in the series R-382[1] of the chick-embryo-adapted strain of MEF_1 poliomyelitis virus.

Experimental Procedure.—Yolk Sac Inoculation: Following a technique which has been described,[1] 100 7-day-old embryos were injected with aliquots of 0.3 ml. of a 20% chick-embryo suspension in buffered saline, containing 200,000 mouse $L.D._{50}$ doses of virus.

Intravenous Inoculation: The inoculum was purified and concentrated as follows: A 20% chick-embryo homogenate in buffered saline was centrifuged for 30 minutes at 2000 rpm; the supernatant was precipitated at 0-10 C by addition of methanol to a final concentration of 30%. The precipitate was removed by centrifugation, and the virus was eluted to a concentration of four times the original with buffered saline (M/20 phosphate; M/2 sodium chloride).* Ninety-five 8-day-old embryos were inoculated by the intravenous route[6] with aliquots of 0.2 ml. of the purified inoculum containing 16,000 mouse $L.D._{50}$ doses of virus.

Eggs were incubated at 36 C, candled daily, and the mortality noted (Table 1). Live embryos were harvested, as shown in Table 1, for estimation of the virus content of the tissues, as previously described,[1] and for morphologic examination.

Morphologic Examination.—Living embryos were killed, as shown in Table 1, fixed in Bouin's solution, and embedded in paraffin. Serial coronal sections (6μ thick) were made of the entire central nervous system and posterior root and cranial nerve ganglia. The coronal sections through the

Submitted for publication July 20, 1956.

From the Virus and Rickettsial Section, Lederle Laboratories Division, American Cyanamid Company.

Present address (Dr. Love): Laboratory of Pathology, National Cancer Institute, Bethesda 14, Md.

* Dr. A. W. Moyer carried out the purification of virus.

TABLE 1.—*Disposal and Fate of Chick Embryos Inoculated with Poliomyelitis Virus by the Yolk-Sac and Intravenous Routes**

Hours After Inoculation	No. Found Dead		No. Harvested for Morphologic Study†		No. Used for Virus Titration	
	Yolk Sac	Intravenous	Yolk Sac	Intravenous	Yolk Sac	Intravenous
24	22	79	2	1	4	1
48	0	0	2	2	4	1
66	2	0	3	1	4	1
72	0	0	3	1	3	1
92	4	0	3	0	3	0
96	0	0	3	1	3	1
116	4	0	3	0	3	0
120	0	1	3	1	3	1
144	4	1	0	0	0	1

†Only those embryos which are recorded on Table 2 were studied microscopically.
*Virus was injected by the yolk-sac route in 100 embryos and by the intravenous route in 95 embryos. Embryos not accounted for in the Table were discarded at 144 hours.

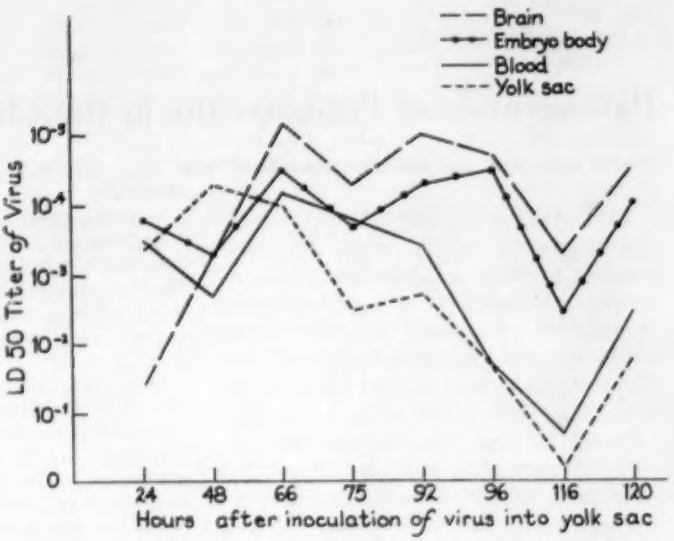


Fig. 1.—Virus distribution in embryos inoculated with 200,000 mouse L.D.$_{50}$ doses of poliomyelitis virus by the yolk-sac route.

body were made posteroanteriorly and included the sympathetic ganglia, heart, and a major portion of the abdominal viscera. Pilot slides were prepared by mounting 1 to 30 sections at intervals of 9 to 29 sections, depending on the size of the embryo; these were stained with hematoxylin and eosin. If, on examination of these slides, a lesion was observed in a ganglion or nucleus without changes in the related ipsilateral or contralateral nucleus or ganglion, every serial section through the latter was stained with Barrett's stain[4] and examined. When any of the spinal ganglia were affected and lesions were not found in the pilot slides of the related area of the cord, every serial section of the cord was examined. In addition, all the serial sections through the olfactory bulbs were studied.

Results

Titration of Virus

Yolk-Sac Inoculation (Fig. 1).—The concentration of virus in the yolk sac reached

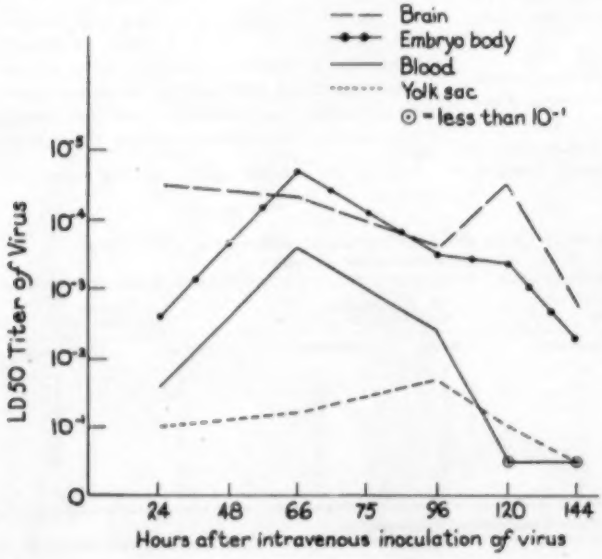


Fig. 2.—Virus distribution in embryos inoculated intravenously with 16,000 mouse L.D.$_{50}$ doses of poliomyelitis virus.

TABLE 2.—*Distribution and Severity of Specific Lesions of the Nervous System in Ten Embryos Inoculated with MEF$_1$ Poliomyelitis Virus on the Seventh Day of Incubation by the Yolk-Sac Route* and in Three Embryos† Inoculated on the Eighth Day by the Intravenous Route‡*

ROUTE OF INOC.	NO	HOURS AFTER INOC.	CRANIAL NERVE NUCLEI AND GANGLIA																CORD & MOT. CERVICAL	
			III N	IV N	V N	V G	VI N	VII N	VII G	VIIIN VESTIB.	VIIIN COCHL.	VIII G	IX G	X N	X G JUG.	X G NODOSE	XII N	N	G
YOLK SAC	1	66	-	-	-	(+)	-	-	-	-	-	-	-	-	-	-	-	-	-
	2	75	-	-	-	(++)	L+	[L+]	-	-	-	-	-	-	-	-	-	-	(+)
	3	75	-	-	-	(++)	-	-	-	-	-	-	-	-	-	-	-	-	-
	4	92	-	-	-	(L+)	R++	[R+]	-	R++	R++	R+	-	-	-	-	-	-	-
	5	92	-	-	+	+++	+	[R+]	-	++	+	+	-	[R++]	(++)	-	-	-	(+)
	6	96	-	-	++	+++	+	[++]	L+	[++]	[+]	L+	-	[+]	+++	-	-	+	++
	7	96	[+++]	-	++	++++	+	+++	++	++	+	+++	-	[++]	+++	R+	+	+	++
	8	116	[+++]	+	++	++++	+++	+++	++	+	++	+++	+	+++	+++	++	+	+	++++
	9	116	[+]	-	++	+++	++	[++]	L++	+++	+	++	++	+++	+++	++	++	+	+++
	10	120	+++	+	+++	++++	+++	+++	++	+++	++++	+++	++	++++	++++	++	+	+	++++
Intravenous	1A	48	[++]	-	+	+++	+++	[+]	-	++	+	+	-	[+]	++	-	-	+	+++
	2A	75	-	-	-	(+)	++	[L++]	-	[++]	[+]	L++	-	-	(L+)	-	-	-	-
	3A	120	-	-	-	(++)	+	[R+]	-	[+]	-	-	-	-	-	-	-	+	+

a maximum 48 hours after inoculation and then fell. The viral content of the blood increased for a short period, dropped, and then rose still higher, before finally falling off slowly; the first and second peaks occurred at 24 and 66 hours, respectively. The amount of virus demonstrable in the brain steadily increased to reach a maximum at 66 hours, after which it decreased slightly. The embryo-body fraction contained considerable amounts of virus 24 hours after inoculation; after a slight drop, the viral concentration of the body followed that of the brain at a slightly lower level.

Intravenous Inoculation (Fig. 2).—Little or no virus (maximum titer 10^{-1}) was demonstrable in the embryos harvested at 48 and 75 hours. For reasons which will be discussed, these embryos probably received negligible amounts of virus and were not included in the Figure.

The viral content of the brain rose rapidly to a maximum at 24 hours and remained high throughout. The concentration of virus in the body was similar to that in the brain. Viremia increased during the first 66 hours and then subsided. Small but definite amounts of virus were demonstrable in the yolk sac after 24 hours.

Morphologic Findings

Macroscopic.—No gross abnormalities were observed in any of the embryos.

Microscopic.—Yolk-Sac Inoculation: No changes attributable to virus infection were found in two embryos harvested at 24 hours, in 2 at 48 hours, and in one at 66 hours, after inoculation of virus. Myocarditis was not seen in any of the embryos.

Specific lesions of the nervous system similar to those which have previously been described in poliomyelitis of the chick embryo [1] were first noted in one embryo 66 hours after infection and were present in all nine embryos which were harvested and examined after that. The incidence, distribution, and some indication of the severity of these lesions are presented in Table 2. In order to condense the Table, the severity of the bilateral lesions is represented by the mean of the damage on both sides. Neuronal degeneration was, however, not infrequently very unequally distributed in bilateral lesions. In spite of some variation in the

GANGLIA LOWER N	GANGLIA LOWER G	SUBSTANTIA RETICULARIS LOWER†	SUBSTANTIA RETICULARIS UPPER†	OLIVARY NUCLEI INF.	OLIVARY NUCLEI SUP.	CEREBELLUM	CORPORA QUADRIGEMINA	SEMILUNAR NUCLEI	OPTIC TECTUM	HYPOTHALAMUS	THALAMUS	STRIATUM ‖	HIPPOCAMPUS	OLFACTORY BULBS
-	(+)	-	-	-	-	-	-	-	-	-	-	-	-	-
-	(++)	-	-	-	-	-	-	-	-	-	-	-	-	-
++	+++	-	-	-	-	-	-	-	-	-	-	-	-	-
++	+++	+	-	-	R+	-	-	-	-	-	-	-	-	-
++	+++	++	+	+	-	++	-	R+++	-	L+	-	+	-	+
+++	++++	+++	+	+	R+	+	+	-	+	L+	L+	+	+	-
++	+++	+++	+++	++	+	+++	+	+	+	+	-	-	+	-
+++	++++	+++	+++	++++	++	+++	++	+++	++	+	+	++	++	+
++	++++	++	+++	+++	+	++	+++	R+++	L+	+	+	+	-	R+
+++	++++	+++	++++	++++	+	++	++	++	++	+	+	++	++	++
++	+++	+	++	++	+	++	+	+	+	+	-	+	+	R++
-	(+)	-	+	-	L+	+	-	L+	-	-	-	-	-	-
++	++++	+	+	-	-	+	-	-	+	-	R+	+	-	-

* No lesions in two embryos killed harvested at 24 hours, two at 48 hours, and one at 66 hours after inoculation.

† No lesions in four embryos harvested at 24, 48, 66, and 96 hours, respectively, after intravenous inoculation.

‡ N = nuclei or anterior horn cells; G, ganglia; +, 2-20 neurones damaged; ++++, more than two-thirds of neurones damaged; ++ and +++, intermediate degrees of damage (in bilateral lesions unless stated otherwise); L, left side only; R, right side only; —, no lesion on either side.

Circle with dot: Brachial, thoracic and lumbosacral cord.
Greek cross: Lower = medulla and pons; upper = midbrain.
Square with dot includes superficial corticoid areas except for hippocampus.
Ovals: Emphasis on damage to a ganglion without lesions in the related nucleus.
Rectangles: Emphasis on damage to a nucleus without lesions in the related ganglion.
Crossed circle: Specific lesions present in the ciliary ganglia of this embryo only.
Crossed S: Lumbosacral and lower thoracic only.

degree of damage at different levels of the spinal cord, the brachial, thoracic, and lumbosacral regions were usually affected simultaneously and have accordingly been grouped together (Table 2).

The earliest lesions were observed in the Gasserian and posterior root ganglia and in the sixth and seventh cranial nerve nuclei (Nos. 1 and 2, Table 2). Lesions of the Gasserian ganglion without any changes in the related nucleus were found in all of the first four embryos (Nos. 1 to 4, Table 2). As in the previous study,[1] the trigeminal ganglion was affected in all the embryos that developed lesions. The motor nucleus of the fifth nerve was involved in one embryo 92 hours after inoculation (No. 5, Table 2) and in all embryos harvested after that (Nos. 6 through 10, Table 2).

Anterior horn cells were first affected in one of the embryos harvested 75 hours after inoculation of virus (No. 3, Table 2). With one exception (cervical cord, No. 5) neuronal degeneration in the spinal ganglia after 75 hours was invariably associated with similar, though less extensive, changes in the related areas of the cord. Lesions were severer in the lumbar, thoracic, and brachial than in the cervical region (Table 2). The amount of neuronal cytolysis in the anterior horn at a particular level could sometimes be correlated with the degree of damage in the corresponding ganglion, but this was not always the case.

Unilateral or bilateral involvement of the sixth cranial nerve nucleus occurred in all but two (Nos. 1 and 3) of the embryos which showed lesions.

Degeneration of the nucleus of the facial nerve associated with a normal ipsilateral geniculate ganglion, as noted in Embryo 2, was seen on four further occasions (Nos. 4, 5, 6, and 9, Table 2). Cytolysis of neurones in the distal and proximal parts of the facial ganglion was first noted 96 hours after inoculation (Nos. 6 and 7, Table 2); thereafter, the ganglion was affected in all but one instance (No. 9, right facial ganglion, Table 2).

The vestibular and cochlear nuclei and the acoustic ganglia were damaged early and frequently (Nos. 4 through 10); in one embryo with bilateral neuronal degeneration (No. 6) the right acoustic ganglion was normal.

Neuronal cytolysis was constant and severe in the jugular ganglion from 92 hours on, and on one occasion no lesion was found in the ipsilateral nucleus of the vagus (left jugular ganglion, No. 5, Table 2). In three embryos one or both ganglia nodosa were normal when lesions were present in the vagal nucleus and jugular ganglion (Nos. 5, 6, and 7).

The glossopharyngeal nucleus could not be distinguished with certainty.[1] Lesions of the petrosal ganglion were not observed until 116 hours after inoculation (No. 8, Table 2). The oculomotor nucleus was involved at 96 hours, and, in one embryo (No. 10), the ciliary ganglion showed lesions which were significantly greater than those which have been described in uninfected embryos.[1] Lesions of the nuclei of the 4th and 12th cranial nerves were late in appearing and were never very extensive (Table 2).

The spread of neuronal changes within nuclei of ganglia did not seem to follow any consistent pattern. Sometimes the earliest lesions were distal and sometimes proximal; in other cases they were peripheral, central, or general. Nor could the order of involvement be related to the distribution of lesions within the ganglion or nucleus in the later stages of infection.

In addition to changes in spinal and cranial nerve ganglia and nuclei, lesions were observed in one embryo 92 hours after infection in the substantia reticularis of the medulla and in the superior olive. From this time on, neuronal damage of considerable degree was frequently present in the substantia reticularis of the medulla, pons, and midbrain, and the olivary nuclei, cerebellum, corpora quadrigemina, semilunar nuclei, and optic tectum (Table 2). Less severe changes were found in the hypothalamic region, thalamus, striatum, hippocampus (area entorhinalis of Rose[5]), and olfactory bulbs (Table 2). In the most severely affected embryos an occasional degenerating neurone was seen in the ganglia of the sympathetic chain (Nos. 6, 8, and 10); the intermediate nucleus of the medulla; the lateral mesencephalic, pretectal, and spiriform nuclei; the nucleus isthmi; nucleus principalis praecommissuralis, and the lateral geniculate bodies. No lesions were observed in the celiac ganglion.

Neuronal degeneration was found in many parts of the forebrain, usually in the form of ill-defined foci, in which practically every neurone was affected. Although no sharp distinction could be made between cortical neurones and the underlying striatum, most of the lesions appeared to be in the corticoid areas (dorsolateral surface area[5]) and in the hippocampal region (Table 2).

Intravenous Inoculation: Only 15 embryos survived more than a few hours after inoculation, and, of these, 7 were available for histologic examination (Table 1). Neuronal degeneration was observed in three of these embryos (Table 2). The character of the lesions was essentially the same as that which followed yolk-sac inoculation, except that hemorrhages were more numerous and more extensive. Myocarditis was not seen. The disease process was considerably accelerated, and extensive pathologic changes were present as early as 48 hours after inoculation (No. 1A, Table 2). In spite of the small amount of virus in the inoculum, neuronal degeneration was more advanced (though not more widespread) 75 hours after intravenous injection (No. 2A, Table 2) than it was in one

of the first series (No. 2) harvested at the same interval after infection by the yolk-sac route. As in the yolk-sac series, there was little inflammatory response in the first two embryos (Nos. 1A and 2A, Table 2). In the third embryo, 120 hours after infection there were a number of vascular and perivascular inflammatory foci, similar to those which have been seen at a much later stage when virus was introduced by the yolk-sac route.[1]

The distribution of neuronal degeneration in the intravenous group was essentially the same as in the yolk-sac series. The Gasserian and spinal ganglia and the sixth and seventh cranial nerve nuclei were affected in every embryo (Table 2). In four instances lesions were present in the Gasserian ganglion, while the ipsilateral trigeminal nucleus was normal (Nos. 2A and 3A, Table 2). Although the facial nucleus was involved four times, no lesions were seen in the geniculate ganglia (Nos. 1A, 2A, and 3A). In one embryo (No. 2A) spinal ganglia were affected and the cord was normal. On three occasions lesions in the nuclei of the eighth nerve were associated with normal ipsilateral acoustic ganglia (Nos. 2A and 3A; cf. No. 6, Table 2). The jugular ganglion was affected without involvement of the vagal nucleus (No. 2A; cf. No. 5).

Neuronal degeneration in the substantia reticularis, olivary nuclei, cerebellum, corpora quadrigemina, semilunar nuclei, olfactory bulbs, and higher centers was comparable in extent to that which accompanied the same degree of damage to the nerve nuclei and ganglia in the yolk-sac series (Table 2). An occasional necrotic neurone in the sympathetic trunk was found in Nos. 1A and 3A, but the celiac ganglia were intact.

Comment

The distribution of pathologic changes and of virus in the chick embryos infected with poliomyelitis virus by the yolk-sac route was similar to that which has been described before[1]; comparison with the previous observations reveals that the earlier onset, greater severity, and more widespread distribution of lesions in the present experiment can be related to the larger amount of virus in the inoculum and the higher virus titers obtained.

In order to make the intravenous series as nearly comparable as possible to the yolk-sac experiment, embryos were inoculated as early as possible, i. e., on the eighth day of incubation. At this age, it was not possible to ensure that the entire inoculum went into the vein, and it was also necessary to reduce the amount of virus in the inoculum. These factors readily explain the absence of lesions and of virus in some embryos and the failure to obtain a graded series of embryos with progressively severer pathologic changes. Nevertheless, the results clearly demonstrate that even small amounts of virus introduced into the blood stream rapidly enter the nervous system (Fig. 2) and produce widespread pathologic changes (No. 1A, Table 2).

During the first 48 hours after infection by the yolk-sac route, increasing amounts of virus were demonstrated in the yolk sac (Fig. 1). At the same time significant virus titers were also recorded in the blood embryo body; after 48 hours the viral content of the yolk sac dropped, while that of the other two fractions rose to higher levels (Fig. 1). Since there was no correlation between the amount of virus in the yolk sac and that in the blood or body (which includes the gastrointestinal tract), the viral increase in the yolk sac must be attributed to local multiplication of virus. On the other hand, the concentration of virus in the yolk sac after intravenous inoculation was much lower and might be derived, at least in part, from the blood or from the gastrointestinal tract. Some late multiplication of virus in the yolk sac may be inferred, because the maximum titer was reached at 96 hours when the titers of the body and blood fractions were falling (Fig. 2).

A significant viremia was established 24 to 48 hours after inoculation of the yolk sac (Fig. 1). The fall in the blood virus

titer which followed cannot be attributed to decreased production of virus by the yolk sac, since the yolk-sac titer continued to rise (Fig. 1). When the virus titer of the blood dropped, the titer of the embryo-body fraction also fell and that of the brain increased (Fig. 1). This temporary decline in blood virus concentration, which has been observed before,[1] is probably not due to removal of virus by the gastrointestinal tract or non-nervous tissues, since this would almost likely be reflected by an increase in the titer of the body fraction. Immediately after intravenous inoculation the concentration of virus must have been high in the blood and low in the brain. During the first 24 hours of incubation the virus titer of the brain increased rapidly and, to judge from the low titer of the blood at this time, that of the blood must have fallen (Fig. 2). After intravenous inoculation, therefore, the onset of the primary fall in the virus concentration of the blood and the accumulation of virus in the brain was even more rapid than in either of the yolk-sac experiments. The repeated observation of rapidly rising titers in the brain accompanied by some depression of the level of viremia would suggest that virus was being taken up by the nervous system during this period at a greater rate than it was being produced elsewhere. Later, when progressive cytolysis of neurones appeared (yolk-sac inoculum, at 66 hours; intravenous inoculum, at 48 hours) and sustained high virus titers were noted in the brain, the subsequent increase in blood virus concentration may be attributed to production of virus by the nervous system (Figs. 1 and 2).

Assuming that the passage of virus through susceptible neurones in the embryonic nervous system causes microscopically visible lesions, analysis of the distribution of lesions provides further evidence that virus enters the nervous system rapidly and directly from the blood. The olfactory; the 5th, 7th, 9th, and 10th cranial, and the sympathetic nerves are all possible routes by which virus might travel from yolk sac and gastrointestinal tract to the nervous system. Direct hematogenous infection must have been responsible for the lesions of the olfactory bulbs which were observed 48 hours after intravenous infection (No. 1A, Table 2). In the yolk-sac series, primary infection of the nervous system by the olfactory route is inconsistent with the early development of lesions in the Gasserian and spinal ganglia and is further precluded by the relatively late and somewhat erratic involvement of the olfactory bulbs (Table 2). The combination of neuronal degeneration in the fifth cranial nerve ganglion and sparing of the fifth nerve nucleus was equally common in the yolk-sac and the intravenously infected embryos and does not, therefore, necessarily imply entry of virus by the trigeminal nerve. Since the geniculate ganglion is susceptible to poliomyelitis infection,[1] centripetal spread of the virus by the seventh nerve would be expected to produce lesions in the ganglion before reaching the nucleus. The seventh nucleus, however, was affected before the geniculate ganglion, irrespective of the route of inoculation, so that infection of the nucleus from the blood is most probable. Entry of virus by the glossopharyngeal nerve is unlikely, because the petrosal ganglion was not affected until very late in the course of the disease (No. 8, Table 2). The distribution of neuronal degeneration throughout the vagus complex seems to preclude spread of the virus by this route. After yolk-sac inoculation, changes in the jugular ganglion not only preceded those in the vagal nucleus (left jugular ganglion, No. 5, Table 2) but also occurred before the more peripheral ganglion nodosum was affected (Nos. 5, 6, and 7, Table 2); a similar phenomenon was also observed after intravenous inoculation of virus (No. 2A, jugular ganglion, Table 2). Spread by the sympathetic nerves is highly improbable, because the celiac ganglion was never affected; although degenerating neurones in the sympathetic ganglia were equally rare in the two groups, they ap-

peared 48 hours earlier in the group which received virus intravenously (cf. Nos. 6 and 1A, Table 2). Finally, the early and frequent involvement of the sixth nucleus, before any neighboring or interconnected structures, can only be attributed to direct hematogenous infection.

After the establishment of the initial lesions, the continued extension of the disease process may be related to two factors—further direct involvement of neurones from the continuing viremia and spread along axis cylinders, as demonstrated by Fairbrother and Hurst.[6,7] The extent to which these mechanisms are operative cannot be accurately assessed. Because lesions appeared simultaneously at many different levels of the spinal cord five days after intracerebral inoculation, Fairbrother and Hurst concluded that axis-cylinder spread was very rapid.[6] Such observations may also be interpreted as the result of dissemination by the blood. In the present experiments certain facts suggest that axis-cylinder spread is relatively unimportant. Very widespread disease was present 48 hours after intravenous inoculation of one embryo (No. 1A, Table 2). Normal ganglia and nuclei were found in the later stages of the disease in close proximity to, or in direct connection with, severely affected neurones. Thus, a normal semilunar nucleus persisted 116 hours after infection, while the right cochlear nucleus, to which it was connected by the lateral lemniscus, was damaged (No. 9, Table 2). In the same embryo, the right facial ganglion was unaffected, and there was severe degeneration of the related seventh nucleus; no spread to the fourth nucleus had occurred from the adjacent oculomotor nuclei or from the vestibular nuclei by the median longitudinal bundle.

The distinctive and consistent pattern of lesions, which was uninfluenced by the route of inoculation, must be attributed to greater susceptibility of neurones, or to some localized difference in the "blood-brain barrier" in these areas. In a recent analysis of the "blood-brain barrier," Waelsch concludes that in embryonic life some substances pass more readily from the blood to the brain than after birth.[8] For example, C^{36} is taken up very slowly by the brain of adult chicks but passes rapidly into the brain of the chick embryo.[8] On the other hand, in rabbits the permeability of the "blood-brain barrier" no trypan blue is no greater in the fetus than in adults.[9] The whole concept of this type of barrier to poliomyelitis in higher animals has been greatly weakened by the recent work of Faber and Dong,[10] who produced widespread disease in monkeys by intra-arterial inoculation of virus, but failed to establish neural infection by the intravenous route. In the latter case, they concluded that some mechanism must have removed most of the virus from the blood before it reached the arterial tree; the virus which was introduced into the arteries must have surmounted the "blood-brain barrier" before passing to the veins, where it would be removed.

Recent theories regarding the pathogenesis of poliomyelitis in primates may now be related to the present study. Local multiplication of virus in the yolk sac, after inoculation of virus by this route, may be compared with the alimentary stage of infection in primates. The lymphoid phase of infection, described by Bodian,[11] cannot exist in embryos in which no lymphoid tissue is present. Viremia follows yolk-sac infection in the embryo and occurs as a primary event after intravenous inoculation of the virus. In the chick embryo, both Verlinde's[12] hypothesis of primary hematogenous invasion of peripheral ganglia and Bodian's,[11] of nuclei, appear to be true. Although centrifugal and centripetal spread of virus along peripheral nerves[13] and axis-cylinder transmission within the central nervous system[6,7] do occur under certain conditions, these mechanisms do not seem to be important in poliomyelitis of the chick embryo. The predominant role of direct hematogenous infection in the extension of the disease in the embryo may be attributed to the prolonged high concentration of virus in the blood. A comparable degree of viremia has not been observed in man.[14] If poliomye-

litis virus is taken up as rapidly by the human nervous system as it seems to be in monkeys,[10] even small amounts of virus in the blood could lead to neural infection. The absence of paralysis in patients with viremia does not necessarily preclude infection of the nervous system, or even cytolysis of neurones.[15] Nevertheless, a fuller understanding of the nature and importance of the "blood-brain barrier" to poliomyelitis virus and of the factors which influence it will be necessary to evaluate the importance of direct hematogenous infection of the nervous system in man.

Summary

The development of pathologic changes and the distribution of virus are described in chick embryos infected by the yolk-sac and intravenous routes with egg-adapted MEF_1 poliomyelitis virus.

The distribution and character of the lesions are independent of the route of inoculation. Cytolysis of neurones is first noted 66 hours after inoculation of yolk sac with 200,000 mouse $L.D._{50}$ virus, and 48 hours after intravenous administration of 16,000 mouse $L.D._{50}$ virus. The earliest histologic lesions are observed in the Gasserian and posterior root ganglia and in the nuclei of the sixth and seventh cranial nerves, at which time the trigeminal nuclei, cord, and geniculate ganglia appear normal.

The concentration of virus in the nervous system rises much more rapidly after intravenous than after yolk-sac inoculation. Twenty-four hours after intravenous administration of virus the titer of virus in the brain is $10^{-4.5}$ $L.D._{50}$; this level is not attained until 66 hours after a greater amount of virus is given by the yolk sac route.

The pathogenesis of poliomyelitis in chick embryos is interpreted as follows: After injection into the yolk sac, virus proliferates and initiates a viremia; from the blood, virus enters directly into the nervous system at many widely scattered points, where it multiplies, produces lesions, and supplements the preexisting level of viremia. The initial localization and the continued extension of the disease process appear to be attributable to the relative susceptibility of neurones to infection from the blood; transmission of virus along peripheral-nerve pathways does not seem to play any significant part. Virus which has been inoculated into the blood passes directly to the nervous system, where it initiates the changes described.

The results are interpreted in the light of the peculiarities of the chick embryo and are related to the observations of other investigators on the pathogenesis of poliomyelitis in higher animals.

Eugenia E. Berry and Marie J. Warford gave technical assistance.

National Cancer Institute (14).

REFERENCES

1. Love, R., and Roca-Garcia, M.: Pathology of Poliomyelitis in the Chick Embryo, Am. J. Path. 31:901-931, 1955.

2. Roca-Garcia, M.; Moyer, A. W., and Cox, H. R.: Poliomyelitis: II. Propagation of MEF_1 Strain of Poliomyelitis Virus in Developing Chick Embryo by Yolk Sac Inoculation, Proc. Soc. Exper. Biol. & Med. 81:519-525, 1952.

3. Beveridge, W. I. B., and Burnet, F. M.: The Cultivation of Viruses and Rickettsiae in the Chick Embryo, Medical Research Council, Special Report Series No. 256, London, His Majesty's Stationery Office, 1946, pp. 22-23.

4. Barrett, A. M.: A Method for Staining Sections of Bone Marrow, J. Path. & Bact. 56:133-135, 1944.

5. Huber, G. C., and Crosby, E. C.: The Nuclei and Fiber Paths of the Avian Diencephalon, with Consideration of Telencephalic and Certain Mesencephalic Centers and Connections, J. Comp. Neurol. 48:1-225, 1929.

6. Fairbrother, R. W., and Hurst, E. W.: Pathogenesis of, and Propagation of the Virus in Experimental Poliomyelitis, J. Path. & Bact. 33: 17-45, 1930.

7. Bodian, D., and Howe, H. A.: Neuronal Pathways as Determining Factors in Dissemination of Poliomyelitis in the Central Nervous System, Proc. Soc. Exper. Biol. & Med. 41:540-545, 1939.

8. Waelsch, H.: Proceedings of First International Neurochemical Symposium, edited by H. Waelsch, New York, Academic Press, Inc., 1955, pp. 187-201.

9. Gröntoft, O.: Blood-Brain Barrier, in report of International Congress of Neuropathology, Lancet 2:668, 1955.

10. Faber, H. K., and Dong, L.: Studies on Entry and Egress of Poliomyelitis Infection: VIII. Relation of Viremia to Invasion of the Central Nervous System, J. Exper. Med. 101:383-389, 1955.

11. Bodian, D.: Emerging Concept of Poliomyelitis Infection, Science 122:105-108, 1955.

12. Verlinde, J. D.; Kret, A., and Wyler, R.: The Distribution of Poliomyelitis Virus in Cynomolgus Monkeys Following Oral Administration, Tonsillectomy, and Intramuscular Injection of Diphtheria Toxoid, Arch. ges. Virusforsch. 6: 175-182, 1955.

13. Tatsumi, M., and Kawakami, K.: Histopathological Changes of the Peripheral Nervous Ganglia in Experimental Poliomyelitis, Bull. Osaka M. School 1:17-23, 1954.

14. Bodian, D., and Paffenbarger, R. S.: Poliomyelitis Infection in Households: Frequency of Viremia and Specific Antibody Response, Am. J. Hyg. 60:83-98, 1954.

15. Bodian, D., and Howe, H. A.: Non-Paralytic Poliomyelitis in the Chimpanzee, J. Exper. Med. 81:255-274, 1945.

News and Comment

ANNOUNCEMENTS

Additions to "Atlas of Tumor Pathology."—In the American Registry of Pathology from the Armed Forces Institute of Pathology the following fasicles have been added to the "Atlas of Tumor Pathology":

(*a*) "Tumors of the Eye and Adnexa," by Dr. Algernon B. Reese, has been completed and is now available.

(*b*) "Tumors of the Parathyroid," by Dr. Benjamin Castleman, previously out of print, has been reprinted and is again available.

Pathology of Diseases of Laboratory Animals.—A postgraduate short course on the Pathology of Diseases of Laboratory Animals will be given at the Armed Forces Institute of Pathology from Dec. 10 through Dec. 14, 1956. Further information can be obtained from the Armed Forces Institute of Pathology, Washington 25, D. C.

American Association of Blood Banks.—Eight hundred nineteen delegates attended the Ninth Annual Meeting of the American Association of Blood Banks, which met jointly with the Sixth Congress of the International Society of Blood Transfusion Sept. 3-5, 1956, at the Somerset Hotel in Boston.

The following officers of the American Association of Blood Banks were elected at its business session on Sept. 4, 1956:

President, Dr. E. E. Muirhead, Dallas, Texas

President-elect, Dr. Oscar B. Hunter Jr., Washington, D. C.

Vice-president, Dr. Morten Grove-Rasmussen, Boston

Treasurer, Mrs. Bernice Hemphill, San Francisco (reelected)

Secretary, Miss Marjorie Saunders, Dallas, Texas (reelected)

District Directors also elected were Dr. Mark F. Lesses, Boston; Dr. James Patterson, Tampa, Fla.; Dr. John R. Schenken, Omaha; (reelected) Dr. Owen F. Thomas, Santa Rosa, Calif.

Hyalinosis of Skin and Mucous Membranes (Urbach-Wiethe's Lipoid-Proteinosis)

Histochemical Study of a Case Twenty-Eight Years After Its First Publication

H. UNGAR and I. KATZENELLENBOGEN, Jerusalem

Urbach and Wiethe, in 1929, described a syndrome which consisted of disseminated areas of hyalinosis and lipid deposits in the dermis, the oral mucosa, and the larynx.* About 50 cases of the syndrome are now on record, including several observed before Urbach and Wiethe's description but not properly recognized.†

Until 1954, when Weyhbrecht and Korting [5] for the first time applied the periodic acid-Schiff method in the study of the hyaline change in the dermis, little had been added to Urbach's histological description. The reports have been repetitive and do not clarify whether this rare disease is another example of a generalized lipoidosis or the result of disturbed protein metabolism, possibly related to primary amyloidosis.

This article reports observations made with the aid of recent histochemical methods on a series of biopsy specimens in one of Urbach's original cases in which the disease was identified by one of us (I. K.) 28 years after first being described.* A detailed clinical report and a discussion of clinical laboratory studies are published elsewhere.

Report of Case

Clinical History.—A woman (P. K. in Urbach's articles), aged 56, married, was referred to the skin clinic of the Labor Sick Fund in Jerusalem on account of pruritus vulvae. At the age of 18 the patient had been treated for "rheumatic arthritis." Then, at the age of 28, "latent diabetes" was diagnosed, while the patient was under the observation of E. Urbach, in Vienna.

The skin condition discovered and studied at that time had developed slowly since the age of 10 years and was essentially similar to that described below.* However, over the course of years the lesions had become more widespread, and recently shallow ulcers had appeared in several areas of the skin and the oral and vaginal mucosae.

On examination in 1954, yellowish nodules, 1 to 3 mm. in diameter, covered the skin of many areas, including the entire face, particularly around the eyes (Fig. 1), the neck, trunk, armpits, and several fingers. Below the elbow joints and over the areas of the tibial tuberosities confluent hyperkeratosis was present, in addition to the yellowish nodules.

The skin of the face, neck, and back was pitted, wrinkled, and covered with innumerable small scars. The hair was absent over all areas containing nodular or scarred lesions. The hair of the scalp was sparse, and the eyelashes were missing.

The oral mucosa, beginning at the lips, was studded with yellowish papules and small elevated plaques of firm consistency. The lesions were especially numerous on the labial mucosa, and the mucosa along the frenulum of the tongue and the uvula was also thickened by raised, yellowish plaques.

Laryngoscopy (reported by Dr. J. Simha) revealed lesions along the borders of the vocal cords which were similar to those in the oral mucosa.

Physical Examination (Dr. L. Nelken): Examination of the heart revealed systolic murmurs over all areas, but no abnormalities either on fluoroscopy or in the electrocardiogram. The blood pressure was within normal limits. Physical and roentgenologic examinations of the lungs and the alimentary tract showed no pathological changes.

Laboratory Examinations: The urine contained occasional traces of albumin and a few white and red blood cells. At the time of observation mild

Submitted for publication July 18, 1956.

From the Department of Pathology of the Hebrew University-Hadassah Medical School, and the Skin Department, Kupat Holim.

* References 1, 2.

† References 3-7.

Fig. 1.—Nodular and scarring lesions of face. Note the absence of eyelashes and the sparse brows.

glycosuria was present. Blood counts were within normal limits.

Fasting blood sugar, on the first examination at the clinic, was 178 mg. per 100 cc. After dietary control and insulin treatment over a period of three weeks, the glucose level became stabilized at about 130 mg. per 100 cc.

Serum cholesterol and phospholipids were normal or somewhat above the upper limit of the normal; on one occasion cholesterol was found to be 440 mg. per 100 cc. and phospholipids 376 mg. per 100 cc. Plasma proteins were normal. Electrophoretic studies were performed and will be discussed elsewhere.‡

Histological Examination.—Material and Methods: Five biopsy specimens of typical advanced skin lesions and one from an area of skin 10 to 12 cm. from a typical lesion and apparently less involved, were taken over a period of about six months (areas of the shoulder joint, upper arm, thumb, and finger).

Two biopsy specimens of areas containing small nodular lesions were taken from the oral mucosa.

One biopsy specimen from the skin was fixed in Zenker-acetic acid solution, and the remainder were fixed in Baker's 10% formalin solution (containing 1% each of calcium chloride and cadmium chloride).

Frozen sections of formalin-fixed material were examined in polarized light or stained as follows: Sudan IV, Sudan black, Baker's acid-hematein method for phospholipids, and Schultz' method for cholesterol.

Paraffin sections were stained with Mayer's hematoxylin and eosin, Van Gieson's method, Heidenhain's azocarmine, Weigert's method for elastic fibers, Laidlaw's silver method, Congo red and gentian violet for amyloid, aqueous toluidine blue (0.5%), McManus' periodic acid-Schiff method (PAS), the colloidal iron method [8] and the ninhydrin-Schiff method, controlled by treatment with Schiff's reagent only.[9]

For further identification of PAS-positive substances, the following tests were performed: (*a*) acetylation test according to McManus and Cason,[10] (*b*) incubation with saliva for one hour at 37 C and subsequent staining with PAS; (*c*) treatment of deparaffinized sections with lipid solvents for 18 hours at 37 C before staining (pyridine, methanol-chloroform, and ethyl ether).

Histological Findings: In the areas of fully developed lesions the epidermis showed noncharacteristic verrucous changes and occasional acanthosis.

The essential lesions were observed in the dermis. In the fully developed lesions the dermis was hypertrophic; the subepidermal and papillary strata appeared homogeneous and poorly cellular, staining intensely and diffusely with eosin. The tissues in these areas included numerous distended or slit-like capillary spaces, which were lined by flat endothelial cells and did not show distinct walls (Fig. 2). They were occasionally surrounded by histoid or lymphoid cells.

The biopsy specimen which had been taken at some distance from a focus of hyperkeratosis (in future called the "early lesion") revealed that the hyaline transformation of the dermis was limited to the

‡ Katzenellenbogen, I., paper to be published.

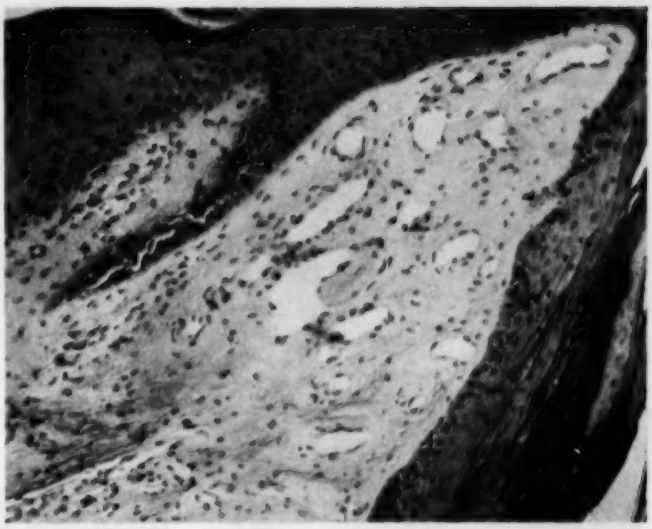


Fig. 2.—Late lesion, showing hyperkeratosis. The dermis contains wide-open blood spaces, the walls of which have merged with the surrounding hyalinized tissue. Hematoxylin-eosin; × 120.

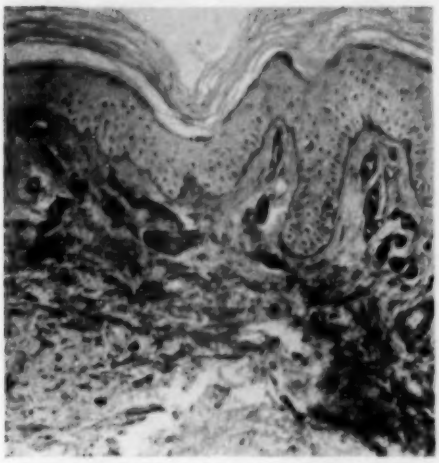


Fig. 3.—Early lesion: hyalinization of arterioles in the papillary zone of the dermis. Colloidal iron method, followed by periodic acid-Schiff procedure; reduced to 77% of mag. × 135.

walls of capillaries within the capillary bodies (Fig. 3).

Severe changes were observed in the sweat glands, the epithelial elements showing various degrees of atrophy and the tubules being dislocated or replaced by hyaline material (Fig. 4). Adjacent to the glands hyaline changes were observed, which showed no clear delineation. There were also several arterioles nearby showing hyalinosis of the vessel walls.

In the "early lesion" the sweat glands revealed no hyaline deposits; the glandular epithelium was preserved, but the distance between the tubules appeared to be widened and the spaces contained metachromatic material.

The intermediate layers of the dermis appeared mainly unaffected in hematoxylin-eosin sections. There were frequent infiltrations of small histiocytes around capillaries, which generally appeared increased in num-

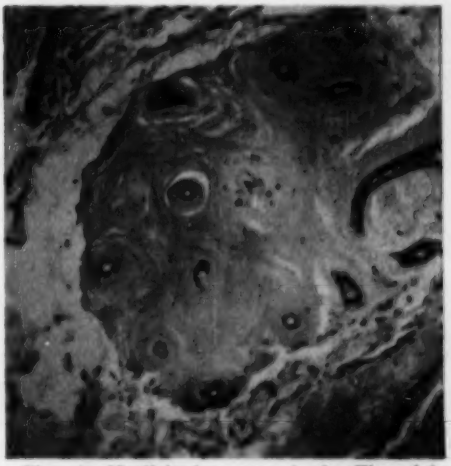


Fig. 4.—Hyalinized sweat gland. The right lower quadrant of the picture shows hyalinization of tissue surrounding the gland. Hematoxylin-eosin; reduced to 77% of mag. × 125.

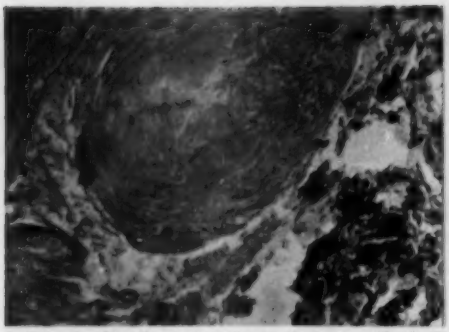


Fig. 5.—Hyalin nodule in oral mucosa. Periodic acid-Schiff procedure; × 130.

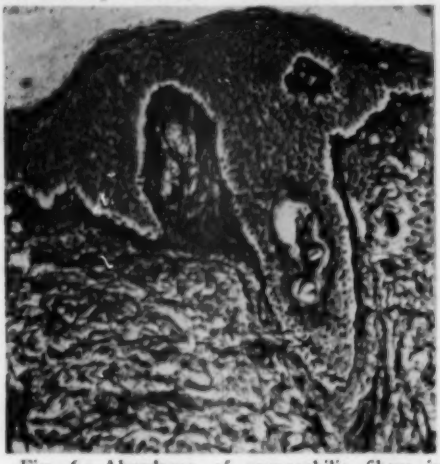


Fig. 6.—Abundance of argyrophilic fibers in section from area of early lesion. Laidlaw's method; reduced to 77% of mag. × 130.

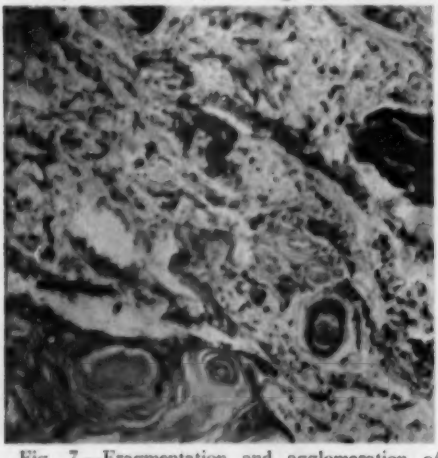


Fig. 7.—Fragmentation and agglomeration of elastic fibers in the dermis. A hyalinized sweat gland if seen in the left lower corner. Weigert's elastica stain; reduced to 84% of mag. × 130.

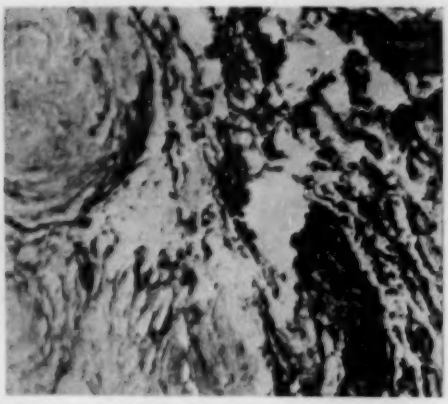


Fig. 8.—Fragmented and clumped elastic fibers in the oral mucosa near hyaline node. Weigert's elastica stain; reduced to 84% of mag. × 130.

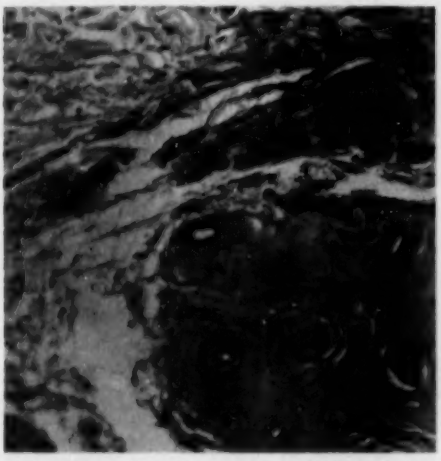


Fig. 9.—Positive stain for amyloid in hyalinized area near sweat gland. Congo red; reduced to 77% of mag. × 125.

ber. Occasional isolated islands of hyalinized fibers were observed, the origin of which is discussed below.

In biopsy specimens from the oral mucosa the epithelial covering was moderately hyperplastic and no keratinization was observed. The tunica propria contained hyaline nodes, which were round or lobulated (Fig. 5). These nodes were almost devoid of nuclei, and no conclusion could be drawn regarding their relationship to any glandular structures.

In Van Gieson's stain the hyaline areas in all biopsy tissues were yellowish, with

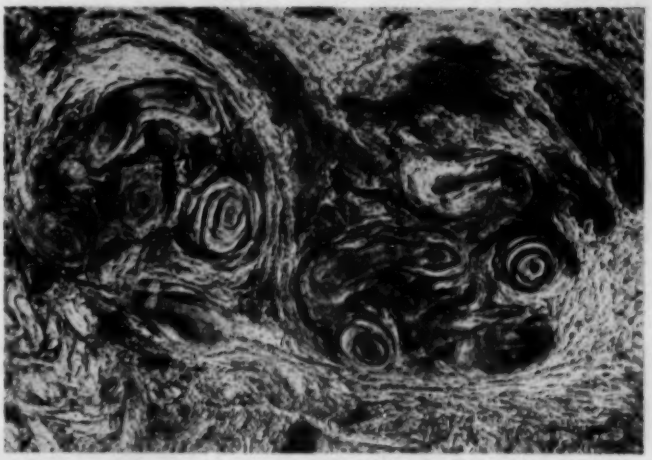


Fig. 10.—Fat stain in hyalinized sweat gland. Sudan black; × 105.

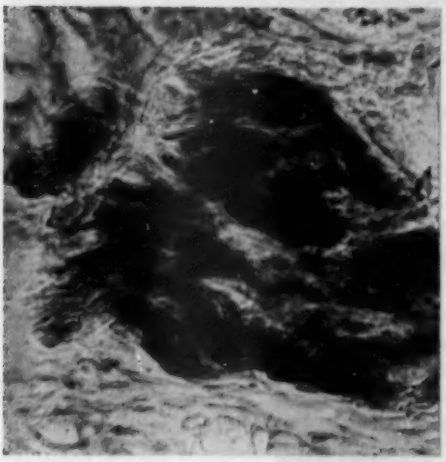


Fig. 11.—Fat stain in clusters of degenerated elastic fibers. Sudan black; reduced to 84% of mag. × 450.

scattered red fibers. The azocarmine method stained the same areas reddish, with isolated blue areas.

Special Histological Stains: Laidlaw's silver method revealed argyrophile fibers in great numbers in the upper layers of the dermis in the early and the advanced lesions (Fig. 6). However, the hyaline areas in the sweat glands were devoid of such fibrils.

Elastic fibrils in the dermis and the oral mucosa were diminished or entirely absent, with the exception of rare fragments; but in the intermediate layer of the dermis in the late lesion agglomerations of coarse and clumped elastic fibers were often seen (Fig. 7). Similarly, clusters of degenerated elastic fibers were found in disorderly arrangement in the oral mucosa adjacent to the hyaline nodules (Fig. 8).

The Congo red stain in paraffin sections was positive for amyloid in areas adjacent to hyalinized sweat glands (Fig. 9) and the hyaline nodes in the oral mucosa, and also within the dermis in the clusters of elastic fibers, described above. The same areas took a metachromatic stain with gentian violet and with aqueous toluidine blue.

Frozen sections stained with Sudan IV and with Sudan black showed the following changes: In the late lesion, either only fine droplets of sudanophil fat were found in the papillary bodies of the dermis in small amounts or it was entirely absent. The hyalinized sweat glands revealed a varying amount of fats surrounding the glandular tubules, visible in somewhat larger amounts with Sudan black than with Sudan red (Fig. 10). Small blood vessels frequently contained fat in subendothelial location.

A remarkable finding was that of sudanophil substance within the clusters of coarse, disorganized fibrils, which were sharply defined and corresponded in location and outline to the islands of degenerated elastic

fibers observed in paraffin sections (Fig. 11).

In sections from the early lesion only a small amount of sudanophil fat was attached to fibrillar structures in the papillary bodies and in the subendothelial layers of arterioles.

In the layers of the epidermis where cellular infiltrations were seen, a great number of small histoid elements contained minute fat granules within the cytoplasm.

Examination of unstained frozen sections in polarized light showed no birefringence. Baker's acid-hematein method for phospholipids and the Schultz test for cholesterol and cholesterol esters were negative. No sudanophil material was preserved in paraffin sections which were passed through alcohols and benzene at room temperature.

Histochemical Methods: Schiff's reagent used without prior treatment gave negative results. The periodic acid-Schiff method used according to the McManus technique stained the hyaline masses intensely red; the stain was diffuse in the papillary bodies; in the nodes in the oral mucosa it was of irregular intensity, and in the sweat glands the color was more or less intense in concentric rings around the remnants of glandular tubules.

No change in the results of the McManus method was seen following incubation with saliva, thus demonstrating the absence of glycogen. Extraction of the sections at 37 C for 18 hours with pyridine or with equal parts of methanol and chloroform or ethyl ether did not produce any change.

Staining was uniformly abolished by acetylation for 45 minutes and completely reestablished by subsequent treatment with potassium hydroxide.[10]

The McManus method applied to sections from the early lesion showed the wall of capillaries within the papillary bodies to be thickened by a concentric or semilunar mass of homogeneously red material. The walls of blood vessels in the deeper strata, and also the sweat glands, appeared stained in the same fashion as in the normal skin.

The colloidal iron method revealed finely bluish fibrils within hyaline areas of the late lesions but uniformly bluish masses in the walls of the thickened arterioles (Fig. 3), and the concentric rings around glandular tubules described above appeared bluish-purple (fig. 12).

The ninhydrin-Schiff test was negative or gave a pale pink stain in all hyaline areas, while the collagen bundles of the dermis were an intense red (Fig. 13 *A*, *B*).

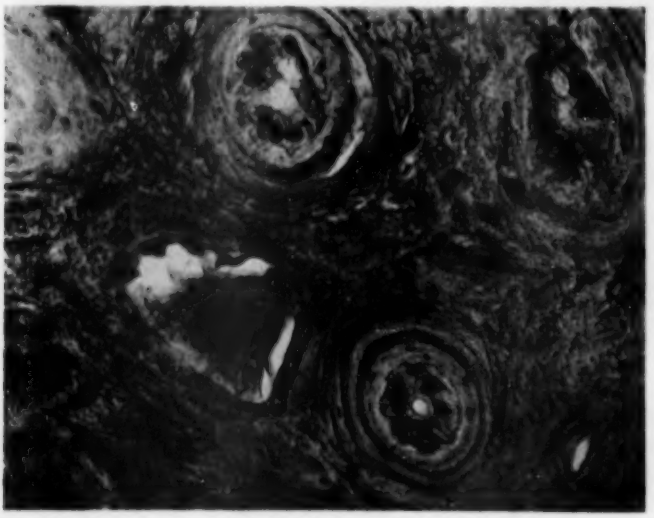


Fig. 12. — Hyalinized sweat gland. Concentric rings and delicate fibrils staining blue with the colloidal iron method. × 500.

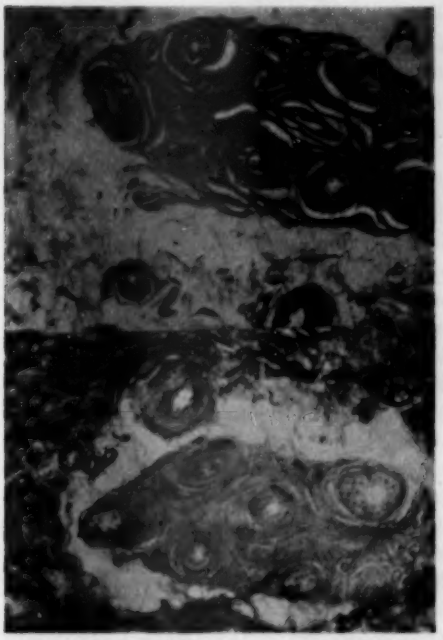


Fig. 13.—Early lesion. Two consecutive sections of sweat gland with hyalinosis. A, The periodic acid-Schiff method demonstrates intense staining of hyalin. B, The ninhydrin-Schiff procedure shows positive reaction of collagen fibers, whereas the hyalin remains unstained. × 140.

Comment

The structural changes in our case corresponded in general with those described in the literature as "lipoid-proteinosis." In addition, we have found a progressive and severe hyalinosis of the sweat glands, which was first recognized by Roessle [11] in one of the earliest cases. This lesion was overlooked for many years and has only recently been adequately described.§ Our case will be discussed with regard to the fat deposits and the nature and pathogenesis of the hyalin.

Nature of Fat Deposits.—Since Urbach's review, in 1932, on the then known cases,[13] the presence of lipids within the tissue lesions has been considered by most authors to be an expression of a disturbance of lipid metabolism.‖ Urbach, when studying our patient and later cases, characterized the deposits as phospholipids from the results obtained by staining with Nile blue sulfate and Sudan IV and the property of dissolving only in hot acetone, but not in cold alcohol. The various hues obtained with these fat stains have since been shown to be devoid of diagnostic value, and, in agreement with Weyhbrecht and Korting [5] we have found that the intra- and extracellular sudanophil material was soluble in ethanol at room temperature. It appears that during the time that has elapsed since Urbach studied the case, the fat deposits have changed their character not only in amount but also in quality, and are now composed probably of neutral fats.

This conclusion is further supported by the negative results of Baker's acid-hematein method for phospholipids, the Schultz reaction for cholesterol, and the absence of anisotropic crystals in unstained frozen sections. The absence of lipids was further confirmed in the results of the periodic acid-Schiff procedure. Since this method may also reveal phospholipids,[18] an undiminished intensity of the stain after previous treatment with hot solvents excluded with reasonable certainty the possibility that such lipids had contributed to the intensity of the stain. All these findings thus agree with the authors who doubted the existence of a lipoidosis either from the results of chemical analysis of the affected skin, which revealed it to contain not significantly more lipids than does normal skin,[19] or from solution experiments with Sudan-stained histological sections.[5]

Nature of the Hyaline Deposits.—The most widespread pathological lesion was the presence of abundant argyrophil fibrils in the upper and middle strata of the dermis, from which, normally, they are practically absent. The reappearance of reticulin fibrils probably represented the earliest demonstrable stage in the disease process, being also present in the biopsy specimen in which as yet hyalinization was seen in the capillary walls only. The argyrophilic transformation

§ References 5, 12.
‖ References 14-17, 6.

of the dermal connective tissue was accompanied by metachromatic staining and by an occasional positive stain with Congo red. These staining qualities were infrequently observed in the late hyaline lesions of the Urbach-Wiethe syndrome by previous investigators but were not considered to be of particular significance.[15]

They appear, however, to be relevant in our case, in which metachromasia was present within papillary bodies and the sweat glands in the biopsy specimen from the early lesion, precisely the areas which eventually showed the greatest extension of hyalin. No metachromasia is normally found in these areas.[20] A similar distribution of positive staining with the colloidal-iron method suggests the presence of polysaccharides containing acidic rests. In areas of fully developed hyalin no such evidence for acidic rests was obtained, and thus their presence appeared to be a transient stage in the formation of hyalin.

The intense staining of the hyaline areas with the periodic acid-Schiff procedure was reestablished by hydrolysis with potassium hydroxide following acetylation.[10] Concomitantly, the hyalin scarcely reacted with the ninhydrin-Schiff method. These results made it unlikely that proteins were included in significant amount in the hyalin compound, which thus appeared to consist mainly of carbohydrates. This observation is complemented by the results of a recently reported chemical analysis of one type of skin hyalin, revealing its probable composition of amino sugars and sulfates in the absence of amino acids.[21]

Possible Pathogenesis of Tissue Lesions.—Urbach and Wiethe and their followers maintained that the sudanophil deposits and the hyaline changes resulted from the seeping in of fatty and protein materials from the blood plasma. However, the location of neutral fat in plaques of degenerated elastica and along the course of hyalinized fibers in poorly vascularized areas of the dermis suggests the origin to be in degenerated fibers of collagen and elastic tissue, which normally contain bound fatty substances.¶ Moreover, it should be noted that, normally, sweat glands contain considerable amounts of sudanophil material,# and there is no need to assume their permeating from the systemic circulation.

Similarly, it appears likely that the hyaline changes described are the result of faulty metabolism of collagen and elastic fibers, leading to the unmasking of carbohydrates. Weyhbrecht and Korting, discussing this possibility, nevertheless continued to argue the "blood-borne" nature of hyalinosis in the Urbach-Wiethe syndrome, mainly because of the centrifugal extension of hyalinosis from the blood vessels in the early stages. They found support for the hypothesis in previous model experiments, in which immersion of collagen tissue in blood serum had resulted in apparent adsorption of proteins and the physical change characteristic of hyalin tissue.[26] Earlier, Roessle considered the homogenizing sclerosis of the dermis, sweat glands, and capillaries in the disease discussed here to be the result of a mild protracted serous inflammation.[11]

Although interference with the fluid exchange may feasibly affect the structure of fibrillary connective tissue, recent histochemical studies and in vitro experiments with human tissues seem to corroborate the view that the hyalin originated in a chemical change of the collagen and elastic fibers. Taylor[27] demonstrated the metachromatic change in early arteriosclerosis to be a result of disintegration of the elastic layer in the vascular wall; likewise, histochemical studies in arteriolar sclerosis have suggested that the hyaline change resulted from the release of lipids and carbohydrates from the affected vascular tissue.[28] Stoughton and Wells[29] also concluded from observations on the pathological increase of polysaccharides in the dermis, as revealed by the periodic acid-Schiff method, that this is probably the result of their release by diseased fibers rather than of an "inflow of polysaccharides."

¶ References 22-24.

References 20, 25.

Lastly, the result of the ninhydrin-Schiff reaction will be considered. Assuming the adsorption in tissue fibers of materials seeping in from the blood plasma, a greater amount of proteins is to be expected in the hyalin than in the surrounding collagen. This was not the case. The negative ninhydrin reaction adds one more argument against the vascular theory of hyalin formation in Urbach-Wiethe disease.

Summary

A case of so-called "lipoid-proteinosis" was reinvestigated in serial biopsies 28 years after its first publication by Urbach and Wiethe.

The essential lesions were found to be degeneration and destruction of elastic fibers and the appearance of argyrophile fibrils throughout the dermis, hyalinosis of the upper layers of the dermis, beginning around small arterioles of the sweat glands, and nodular hyalinosis of the oral mucosa.

Histochemical study of the hyalin revealed the likelihood of its containing carbohydrates but little or no protein. Acidic rests were probably present in the early period of hyalin formation.

In contrast to the earlier report of the case, no lipids could now be identified within the moderate quantity of sudanophil material demonstrable by histological methods.

Various hypotheses on the histogenesis of the lesion are discussed.

The photographs were made by Mrs. H. Weinmann.

REFERENCES

1. Urbach, E.: Beiträge zu einer physiologischen und pathologischen Chemie der Haut: V. Über eine familiäre Lipoidose der Haut und der Schleimhäute and Grundlage einer diabetischen Stoffwechselstörung, Arch. Dermat. u. Syph. 157:451-466, 1929.

2. Urbach, E., and Wiethe, C.: Lipoidosis cutis et mucosae, Arch. path. Anat. 273:285-319, 1929.

3. Holtz, K. H., and Schulze, W.: Beitrag zur Klinik und Pathogenese der Hyalinosis cutis et mucosae (Lipoid-Proteinose Urbach-Wiethe), Arch. Dermat. u. Syph. 192:206-237, 1950.

4. Braun, W., and Weyhbrecht, H.: Beitrag zur Klinik und Pathogenese der Hyalinosis cutis et mucosae (Lipoid-Proteinose [Wiethe-Urbach]), Arch. Dermat. u. Syph. 194:538-554, 1952.

5. Weyhbrecht, H., and Korting, G. W.: Zur Pathogenese der Hyalinosis cutis et mucosae, Arch. Dermat. & Syph. 197:459-478, 1954.

6. Tomkins, J., and Weinstein, I. M.: Lipoid Proteinosis: Two Case Reports Including Liver Biopsies, Special Blood Lipid Analyses and Treatment with a Lipotropic Agent, Ann. Int. Med. 41:163-171, 1954.

7. Izaki, M.; Horiuchi, T., and Hozaki, H.: Lipoidosis Cutis et Mucosae (Lipoidproteinose Urbach-Wiethe): Report of a Case, Keio J. Med. 3:163-177, 1954.

8. Rinehart, J. F., and Abul-Haj, S. L.: An Improved Method for Histologic Demonstration of Acid Mucopolysaccharides in Tissues, A. M. A. Arch. Path. 52:189-194, 1951.

9. Yasuma, A., and Ichikawa, T.: Ninhydrin-Schiff and Alloxan-Schiff Staining, J. Lab. & Clin. Med. 41:296-299, 1953.

10. McManus, J. F. A., and Cason, J. E.: Carbohydrate Histochemistry Studied by Acetylation Technique, J. Exper. Med. 91:651-654, 1950.

11. Roessle, R.: Dystrophia pachydermica cutis et mucosae hereditaria, Arch. sc. med. 50:155-183, 1927.

12. Allen, A. C.: The Skin: A Clinicopathologic Treatise, St. Louis, C. V. Mosby Company, 1954.

13. Urbach, E.: Lipoidstoffwechselerkrankungen der Haut, Handbuch der Haut- und Geschlechtskrankheiten, J. Jadassohn, Editor, Berlin, Springer-Verlag, 1932, Vol. 12, Pt. 2, pp. 238-374.

14. Thannhauser, S.: Lipoidoses: Diseases of the Cellular Lipid Metabolism, New York, Oxford University Press, 1940.

15. Wile, U. J., and Snow, J. S.: Lipoid Proteinosis, Arch. Dermat. & Syph. 43:134-144, 1941.

16. Wise, F., and Rein, C. R.: Lipoidosis Cutis et Mucosae (Lipoid Proteinosis of Urbach), Arch. Dermat. & Syph. 37:201-218, 1938.

17. Ramos e Silva, J.: Lipoid Proteinosis (Urbach-Wiethe), Arch. Dermat & Syph. 47:301-326, 1943.

18. Wolman, M.: Staining of Lipids by the Periodic Acid-Schiff Reaction, Proc. Soc. Exper. Biol. & Med. 75:583-585, 1950.

19. Price, H.; LaRosa, W. V., and Settle, E. B.: Lipoidosis Cutis et Mucosae, Arch. Dermat. & Syph. 55:42-51, 1947.

20. Bunting, H.; Wislocki, G. B., and Dempsey, E. W.: The Chemical Histology of Human Eccrine and Apocrine Sweat Glands, Anat. Rec. 100:61-77, 1948.

21. Siebert, G.; Braun-Falco, O., und Weber, G.: Isolierung und chemische Charakterisierung von Hyalin, Naturwissenschaften 42:300, 1955.

22. Lansing, A. I.: Chemical Morphology of Elastic Fibers, Tr. Conference on Connective Tissues, pp. 45-85, 1951.

23. Koletzky, S., and Stecher, R. M.: Primary Systemic Amyloidosis, Arch. Path. 27:267-288, 1939.

24. Windrum, G. M.; Kent, P. W., and Eastoe, J. E.: The Constitution of Human Renal Reticulum, Brit. J. Exper. Path. 36:49-59, 1955.

25. Montagna, W.; Chase, H. B., and Hamilton, J. B.: The Distribution of Glycogen and Lipids in Human Skin, J. Invest. Dermat. 17:147-157, 1951.

26. Müller, E.: Untersuchungen über Wesen und Entstehungsbedingungen des bindegewebigen Hyalins, Beitr. path. Anat. 97:41-80, 1936.

27. Taylor, H. E.: Role of Mucopolysaccharides in Pathogenesis of Intimal Fibrosis and Atherosclerosis of the Human Aorta, Am. J. Path. 29:871-883, 1953.

28. Montgomery, P. O'B., and Muirhead, E. E.: A Characterization of Hyaline Arteriolar Sclerosis by Histochemical Procedures, Am. J. Path. 30:521-531, 1954.

29. Stoughton, R., and Wells, G.: A Histochemical Study on Polysaccharides in Normal and Diseased Skin, J. Invest. Dermat. 14:37-51, 1950.

News and Comment

PERSONAL NEWS

Dr. William H. Bauer Dies.—Dr. William A. Bauer, of the Department of Pathology at St. Louis University of Medicine, died on June 14, 1956, as a result of coronary occlusion.

Dr. William A. J. Crane Comes to University of Chicago.—Dr. William A. J. Crane, lecturer in pathology at the University of Glasgow, Glasgow, Scotland, has joined the staff of the Ben May Laboratory of Cancer Research at the University of Chicago.

Dr. C. P. Rhoads Awarded Walker Prize.—Dr. C. P. Rhoads, of New York, has been awarded the Walker Prize of the Royal College of Surgeons, England, for his contributions to the knowledge and the therapeutics of cancer. Dr. Rhoads was honored because of his "distinguished career as an experimental pathologist," and for his contributions as scientific director of the Sloan-Kettering Institute for Cancer Research and the Memorial Center for Cancer and Allied Diseases, New York.

Pulmonary Fibrosis and Giant-Cell Reaction with Altered Elastic Tissue

Endogenous "Pneumoconiosis"

ROY L. WALFORD, M.D. and LEO KAPLAN, M.D., Los Angeles

Introduction

This study presents the clinical and pathologic features of 12 autopsied cases of a condition in which the lungs reveal peculiar changes associated with altered elastic tissue. The most striking of these changes include hyperplasia, fragmentation, thickening, and intense basophilia of elastic tissue, the presence in the lungs of large numbers of foreign-body giant cells with active phagocytosis of the altered elastic fibers, and pulmonary interstitial fibrosis. We have outlined the principal features of this process elsewhere,[30] under the caption of "endogenous 'pneumoconiosis' associated with altered elastic tissue."

This pathologic picture bears some resemblance to a number of previously described and not always definite entities. Foremost among these we include (1) the pulmonary changes in some cases of advanced mitral stenosis, as well as severe left ventricular failure from other causes,* and (2) idiopathic pulmonary hemosiderosis of children, originally described by Ceelen[5] and thoroughly reviewed by Wyllie and associates.[33]

The etiology of the widespread and destructive pulmonary changes forming the subject of this report is not apparent. We may be dealing with a primary degeneration of elastic tissue or with secondary elastica injury due to one, or indeed to various, causes. It does not appear to be secondary to heart disease or failure, in that three of the severest cases occurred in the absence of any heart disease except cor pulmonale. The pulmonary obstruction producing this cor pulmonale does not appear independent of the condition under consideration. The essential pathogenetic feature appears to be the provocation by altered elastic tissue of a marked sclerosing foreign-body reaction. Vasculature, as well as interstitium, of the lung may be involved. When fully developed, this process leads to severe pulmonary insufficiency.

Materials and Methods

Over the past eight years all routine slides of the lungs from autopsies performed at the Veterans Administration Center were reviewed by one of us. This series comprises approximately 7000 autopsies. Eleven cases were noted to possess the features described in this report. One further case (Case 12) was supplied by Dr. Otto Saphir, Michael Reese Hospital, Chicago. Complete autopsies and detailed clinical histories were available from all cases. Tissue from a lung biopsy performed two years before death was available in one instance (Case 2). In general, only routine, randomly selected samplings from the lungs were available. These were examined by hematoxylin-eosin, Perl's iron, Wilder's reticulin, Masson's trichrome, and Verhoeff's elastica stains, as well as the orcein and resorcin-fuchsin methods for elastica. The possible presence of calcium in the pulmonary lesions was investigated by means of von Kossa's method, and by means of the chelating agent Meurexide, as described by Kaufman and Adams.[38] Pulmonary tissue from two cases was studied for iron and calcium by the technique of microincineration.

Submitted for publication July 16, 1956.

From the Departments of Pathology, University of California School of Medicine at Los Angeles, the Veterans Administration Center, and Mount Sinai Hospital.

* References 19, 20, 28.

Illustrative Cases (Table 1)

Case 1.—A 53-year-old former hard-rock miner from Nevada noted the onset of exertional dyspnea, fatigue, and ankle edema one year prior to death. He was first admitted seven months after the onset of his illness. A 15-lb. diuresis, with marked symptomatic improvement, followed treatment with digitalis and mercurials. He was discharged one month later with the diagnosis of pulmonary emphysema and fibrosis, with secondary cor pulmonale and secondary polycythemia. There followed gradual return of ankle edema and exertional dyspnea and the development of orthopnea and paroxysmal nocturnal dyspnea. He was readmitted eight days prior to death. Physical examination at that time revealed a thin, plethoric and cyanotic, orthopneic, dyspneic white man with a temperature of 99 F and a blood pressure of 112/80. Neck veins and fundal vessels were distended. The liver was enlarged 3 fingerbreadths below the costal margin and was pulsating. The anteroposterior diameter of the chest was increased, and inspiratory intercostal retraction was evident. The lungs were hyperresonant. A loud apical systolic murmur and many extrasystoles were heard. The second pulmonic sound was loud. The patient's fingers were clubbed, and there was a 2+ pitting edema to the knees. An electrocardiogram revealed right ventricular hypertrophy and strain. A chest roentgenogram revealed marked cardiomegaly, with a prominent right heart and pulmonary artery segment, pulmonary emphysema, and pulmonary fibrosis. Urinalysis was normal. A serologic test for syphilis was negative. The hemoglobin was 18.9 gm. per 100 cc. and the hematocrit reading 59%. Ether circulation time was 16 seconds (normal, 3 to 8 seconds), and dehydrocholin (Decholin) circulation time, 40 seconds (normal, 10 to 16 seconds). Sputum cultures showed normal flora. Seven days after admission the patient's cyanosis and respiratory distress increased, and, despite intravenous aminophylline, he required oxygen by mask. He died the following day.

At necropsy, the body was thin but well developed. The heart weighed 420 gm. The right heart was markedly hypertrophied and mildly dilated. The right ventricular myocardium was 1.2 cm. thick. The tricuspid valve was 14 cm. and the pulmonary valve 9.5 cm. in circumference. The venae cavae and pulmonary arteries were dilated. The left heart was normal except for mild valvular dilatation. Only a mild, nonocclusive coronary arteriosclerosis was present. The lungs were mildly emphysematous and diffusely fibrotic. Neither miliary nor coarse silicotic nodules could be seen. The liver weighed 1500 gm. and showed severe chronic passive congestion. The firm, dark-red spleen weighed 200 gm. The brain weighed 1350 gm. The cerebral vessels were only mildly sclerotic. A pink, semitranslucent mottling was noted throughout the cortex and in the white matter of the right frontal lobe. The left cerebellar lobe had a similar appearance.

Microscopically, the lungs showed mild emphysema and diffuse fibrous thickening of septa and alveolar walls. Throughout the lung there was marked basophilia of interstitial elastic fibers and, to a much less degree, of vascular elastic fibers. The altered fibers were thickened, frayed, and fragmented. Numerous foreign-body giant cells within the bulging septal walls had

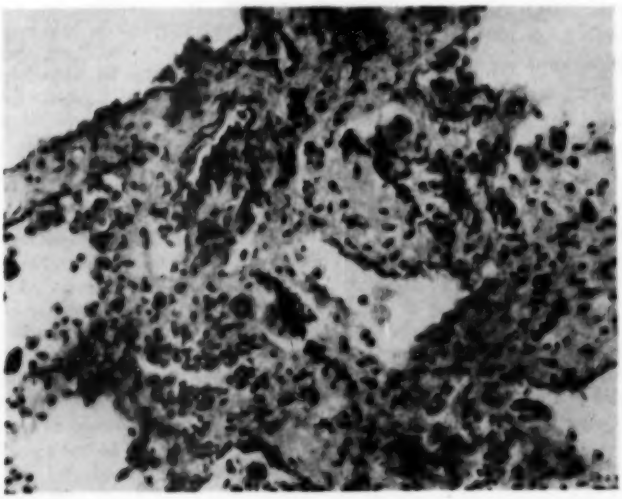


Fig. 1 (Case 2).—Thickened alveolar and septal walls with fragmented basophilic elastic fibers and foreign-body-giant-cell reaction. Hematoxylin and eosin stain; ×120.

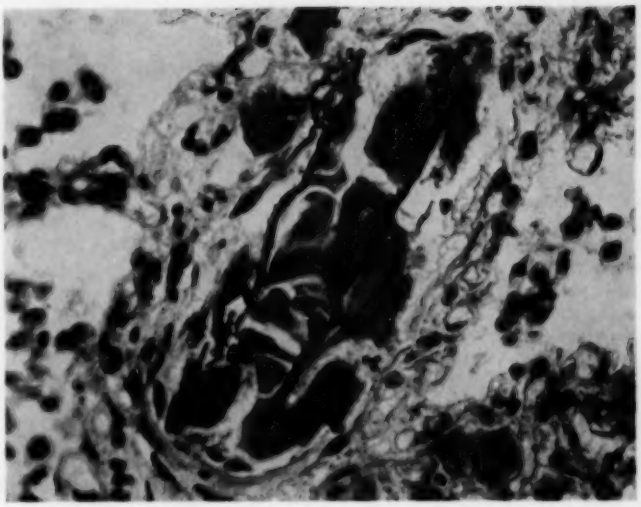


Fig. 2 (Case 10).—Fragments of elastic tissue undergoing phagocytosis by foreign-body giant cells. Note the sharp angulation and fracturing of the brittle-appearing, iron-encrusted fibers. Hematoxylin and eosin stain; × 520.

phagocytosed the altered elastic fibers (Fig. 4). The basophilic elastic fibers, both within and without the giant cells, gave a positive reaction with the Verhoeff, orcein, and resorcin-fuchsin stains, and with Perl's iron stain (Fig. 5). A few of the giant cells contained fine vacuoles, and occasionally stellate inclusions (Fig. 4) (asteroid bodies), giving a positive Verhoeff stain (Fig. 4).

In addition to altered elastic tissue and giant cells, the interstitium of the lungs contained focal accumulations of brown elongated, checkered rods from 5μ to 30μ in length, identical with the iron crystals illustrated in Lendrum's photomicrographs.[19] These gave a positive reaction with Perl's iron stain and a negative reaction with the various elastica stains. Opaque bluish globular bodies, from 5μ to 15μ in size, were also present in the interstitium, often within giant cells, and resembled Schaumann bodies. These were strongly positive with Perl's iron and Verhoeff's elastica stains. With the latter they sometimes showed concentric laminations. Reactions of these

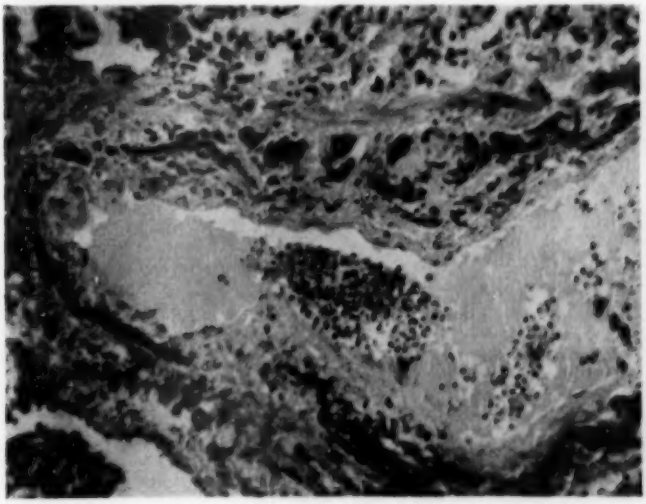


Fig. 3 (Case 12).—The giant-cell reaction to altered elastica takes place both interstitially and within vessel walls. This Figure shows the intramural phagocytic process within a medium-sized vessel. Hematoxylin and eosin stain; × 120.

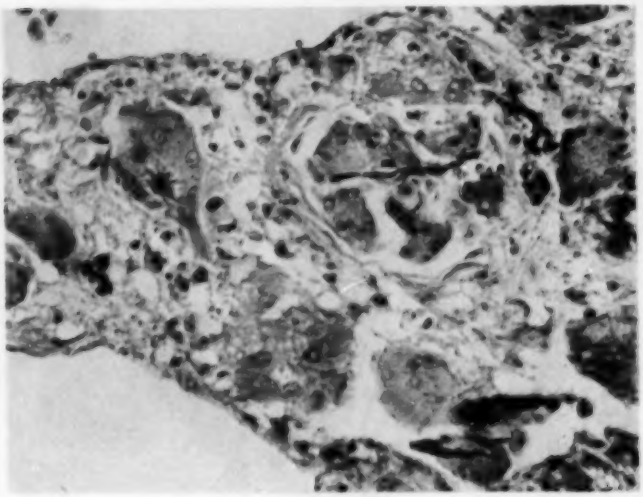


Fig. 4 (Case 1).—Verhoeff's elastica stain of widened septal wall. All phagocytosed fibers take a positive stain. The occasional asteroid body found in this case is also illustrated. × 400.

bodies with the orcein and resorcin-fuchsin stains were equivocal, although the concentric laminations could be seen with both. No plate crystals or epithelioid-cell aggregates were present in the sections. No refractile particles were visible with polarized light.

Except as noted above, iron stains on the lung were negative; specifically, there were only occasional siderophages (heart-failure cells) in the alveoli (Fig. 5). Von Kossa and Meurexide stains for calcium were negative. No calcium could be demonstrated by means of the gypsum reaction performed on microincinerated sections. Yellow-red and deep-red crystals of iron oxide were abundant on microincinerated sections. Besides the lung findings described above, the liver showed a mild cardiac cirrhosis. The cerebrum in all areas revealed early neuronolysis and prominent satellitosis, accompanied by focal vacuolation and edema of the cortex. There was focal loss of Purkinje cells in the cerebellum. These changes were attributed to anoxia.

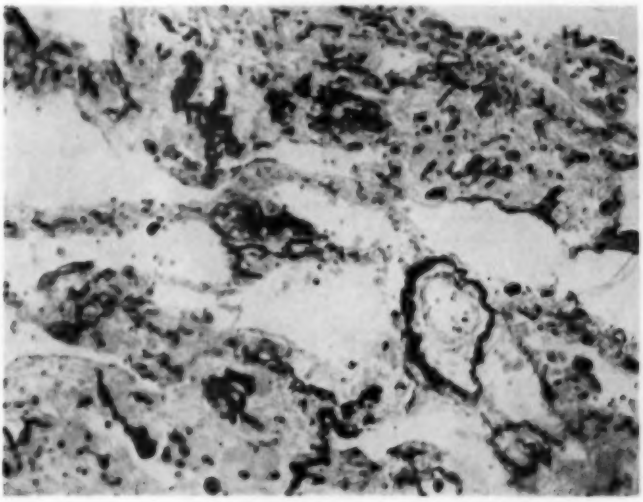


Fig. 5 (Case 1).—Perl's iron stain of lung, revealing iron encrustation of vascular and interstitial elastic tissue. Note absence of siderophagia within the alveoli. × 120.

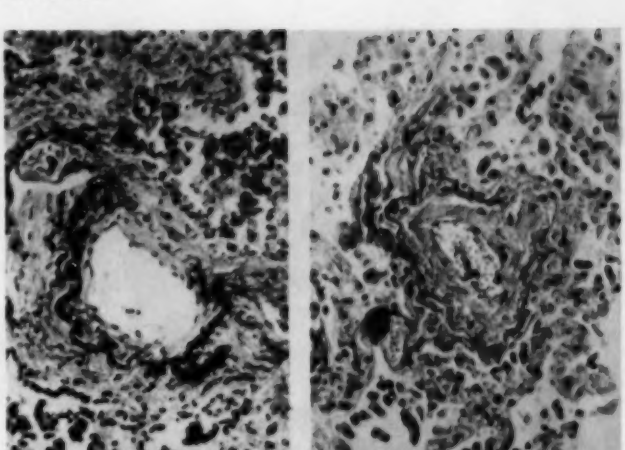


Fig. 6.—The vascular elastic tissue is rendered deeply basophilic by encrustation with iron. Left, Case 12; right, Case 3. In the latter, note the presence of erythrocytes intramurally in the altered vessel wall. Hematoxylin and eosin stain; × 250.

Summary (Case 1).—After a one-year history of increasing dyspnea and cyanosis, this 53-year-old man died of pulmonary insufficiency. Necropsy revealed thickening and bulging of alveolar and septal walls of the lung, associated with frayed and fragmented, intensely basophilic elastic fibers, with deposits of rods and globules of iron-positive material and with marked accumulation of foreign-body giant cells. These changes were responsible for a diffuse pulmonary fibrosis with cor pulmonale and anoxic cerebral damage.

Case 2.—Four and one-half years prior to death this 24-year-old man noted the onset of cough, chest pain, and some fever. He was discharged from military service with the diagnosis of chronic bronchitis, developed progressive exertional dyspnea, and was first admitted three years prior to death. Pulmonary-function and cardiac-output studies indicated diminished pulmonary reserve and a high cardiac output. Two and one-half years before death, or about midway in the course of his illness, a lung biopsy was performed, the sample measuring 2×3 cm. This revealed mild alveolar-wall fibrosis, mild to moderate diffuse increase in the number of mononuclear cells in the alveolar walls, many histio-

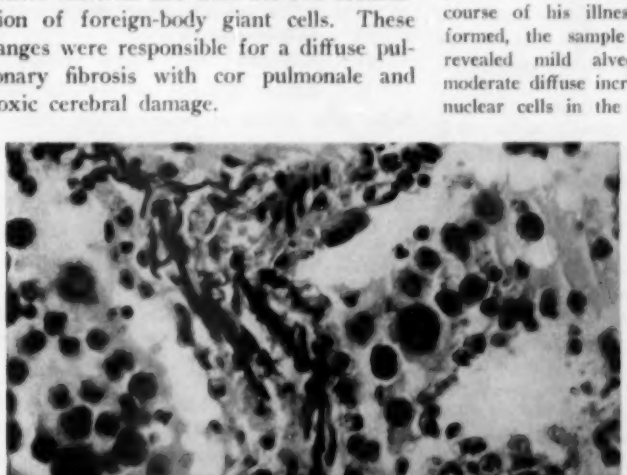


Fig. 7 (Case 12).—Thickened, fragmented, basophilic elastic fibers occupying a central position within an alveolar wall. Hematoxylin and eosin stain; × 420.

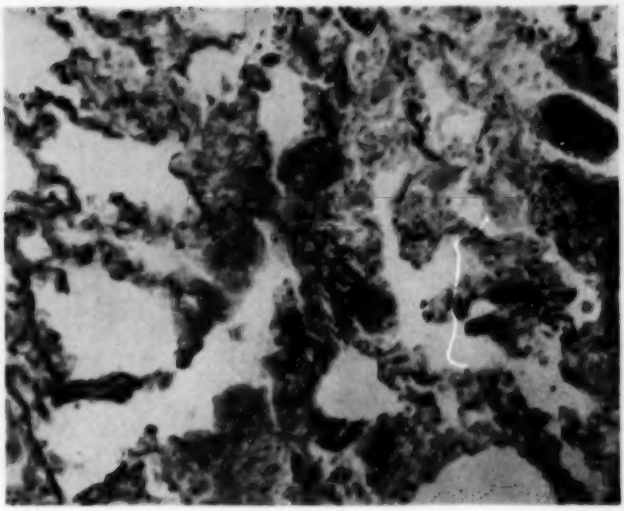


Fig. 8 (Case 2).—Verhoeff's elastica stain revealing marked increase in alveolar and septal elastic tissue in the lung. × 120.

cytes, but little or no hemosiderin within the alveoli. A few giant cells containing hemosiderin and bluish globular bodies were noted in the interstitium. There was rare but intense basophilia of vascular elastic fibers. There was no metaplasia of alveolar-lining cells, such as is prominent in Hamman-Rich disease, no fibrin, and no arteritis, although some of the smallest arterioles contained bland thrombi.

The patient noted occasional episodes of chest pain and slight hemoptysis. He received two courses of cortisone, without benefit. His dyspnea advanced. Cyanosis and cor pulmonale supervened. His final admission was two months before death. At that time he was thin and cyanotic and coughed frequently. Temperature was normal; pulse 120 a minute, blood pressure 80/40. Fingers and toes were clubbed. The white blood cell count was 11,800, with a normal differential. Hemoglobin was 18.9 gm. per 100 cc. and hematocrit 57%. CO_2-combining power ranged between 15 and 20 mEq/liter. Sputum cultures on this, as well as upon many previous occasions, were negative for pathogens. His serologic test for syphilis was negative. Electrocardiograms were typical of right ventricular hypertrophy and strain. Chest x-rays showed an enlarged right heart, prominent pulmonary arteries, and a fine diffuse fibrosis. His vital capacity was 1.54 liters (normal, 3 to 4.5 liters) and the tidal volume 0.92 liter (normal, 0.35 to 0.50 liter). He was treated by phlebotomy, digitalization, and oxygen administration, but became progressively more cyanotic and died.

At necropsy the body appeared cachectic. The heart weighed 500 gm. The right ventricle was greatly enlarged, and the right ventricular myocardium was 1.6 cm. thick. The tricuspid valve was 12.5 cm. and the pulmonary valve 11.5 cm. in circumference. The pulmonary conus was dilated. There was considerable atheromatosis involving the major pulmonary arteries. The left heart was essentially normal. Coronary and aortic arteriosclerosis was minimal. All cut sections of lung revealed a diffuse gray-tan mottling, with some emphysema and focal atelectasis. The liver weighed 1,200 gm. and appeared small, with a very nodular external surface. It showed accentuated markings on section. The spleen weighed 200 gm. and was a dark reddish-brown color.

Microscopically, the lungs revealed a marked diffuse fibrosis of alveolar walls, with mild influx of mononuclear cells into the alveolar walls. There was considerable basophilia, fragmentation, and hyperplasia of the elastic tissue of vessels and alveolar walls (Figs. 1 and 8). The pulmonary fibrosis was intensified in the areas of basophilia. Giant cells, containing elastic fibers and a few bluish globular bodies, were seen. One large and one small artery showed subacute arteritis, characterized by influx of lymphocytes, a few polymorphonuclear leukocytes, and macrophages into the media and adventitia, and a slight smudgy change in the vessel wall. A small artery in the lung showed an obliterative fibroplasia, interpreted as the late or end-stage of an arteritis. Siderophagia was minimal in the sections. The liver showed severe chronic passive congestion and mod-

erate periportal fibrosis. The spleen was congested.

Summary (Case 2).—After a history of progressively increasing dyspnea of four and one-half years, with eventual cyanosis and cor pulmonale, this 24-year-old man died of pulmonary insufficiency. A lung biopsy performed two and one-half years before death revealed mild fibrosis, some mononuclear cells and histiocytes, and scattered basophilic changes in the elastica. Necropsy revealed advanced pulmonary fibrosis associated with typical changes in elastic tissue and accumulation of foreign-body giant cells. Evidence of subacute arteritis and of healed arteritis was found in a very occasional pulmonary vessel.

CASE 3.—A 51-year-old white man had a record of seropositive syphilis for 13 years and known syphilitic heart disease for at least eight years. He had received antisyphilitic penicillin therapy four years before death. His chief complaint on admission was increasing dyspnea, along with orthopnea and ankle edema. There was marked cervical venous engorgement. The pulse was 90 per minute and the blood pressure 130/84. Frequent extrasystoles were heard, as well as loud systolic and soft blowing diastolic aortic murmurs. The liver was enlarged 6 cm. below the costal margin. Venous pressure in the cubital vein was 160 mm. water (normal, 70 to 110 mm. water). Arm-to-tongue circulation time was 35 seconds (normal, 10 to 16 seconds), and arm-to-lung circulation time was 11 seconds (normal, 3 to 8 seconds). Serologic reactions were positive with both Wassermann and Kahn tests. The red blood cell count was 4,500,000 per cubic millimeter. An electrocardiogram revealed an enlarged heart with complete left bundle-branch block. The chest roentgenogram showed a marked cardiomegaly with aortic configuration, a *cor sabot* appearance, and a calcified aneurysmal dilation of the first portion of the aorta. The patient improved considerably with digitalis, quinidine, and mercurials for one and a half to two months, but rather suddenly redeveloped signs of failure, including dyspnea and cyanosis, and died after two days.

At necropsy, the body appeared well developed. There were 4 liters of dark-amber fluid in the peritoneal cavity but no pleural effusion. The heart weighed 900 gm. The enlargement appeared mainly on the left side. The right ventricle was quite dilated, and its wall was 0.5 cm. thick. The dilated tricuspid valve was 15 cm. in circumference. The pulmonary arteries and veins were described as normal. The left ventricle was dilated and hypertrophied. Its wall was 1.4 cm. thick. The aortic valve was sclerotic and calcified, with marked fusion of the anterior leaflets, yielding a bicuspid deformity. The aortic orifice was 1 cm. in circumference. Extending from the posterior sinus of Valsalva to the origin of the right subclavian artery was a saccular aneurysm of the aorta, 7.5 cm. in depth. The portion of the aneurysm involving the sinus of Valsalva appeared ragged and ulcerated. Each lung weighed 500 gm. The lungs were described as appearing grossly normal. The liver weighed 2800 gm. and showed severe passive congestion. The spleen weighed 350 gm. and was intensely congested. The brain revealed an old extensive, traumatic encephalomalacia, involving the frontal lobes.

Microscopically, the aortic valve was greatly scarred and focally infiltrated with lymphocytes. The aneurysmal sinus of Valsalva was the site of a bacterial endocarditis. The myocardium was hypertrophied and focally scarred. No Aschoff bodies were present. The lungs revealed a moderate fibrosis of alveolar walls. There were extensive basophilia and thickening of vascular elastic tissue (Fig. 6, right), with a tendency to wind off into adjacent interstitium. Short, parallel, lamellated strands of deeply basophilic elastic tissue were present in the interstitium. There was clubbing of the ends of alveolar septa. Scattered foreign-body giant cells were present, many containing fragments of elastic fibers. These fragments gave a positive reaction with all the elastica stains. No bluish globular bodies were found. A mild to moderate number of siderophages were scattered through the alveolar spaces. These siderophages were diffuse, and not nodular, in distribution. The liver revealed severe chronic passive congestion. A lipogranulomatosis was noted in the splenic follicular centers. Sections of the brain revealed old malacia.

Summary (Case 3).—A 51-year-old man with a long history of seropositive syphilitic heart disease died of cardiac and pulmonary failure. Necropsy revealed a severe aortic stenosis, aortic aneurysm, bacterial endocarditis of the sinus of Valsalva, and pulmonary fibrosis. The pulmonary fibrosis was associated with basophilia, fragmentation, and thickening of elastic tissue, par-

ticularly the elastic tissue of vessels, and with foreign-body response to this altered elastic tissue.

Case 10.—This 51-year-old white man had a 12-year history of grand mal epileptic seizures, occurring two to three times per month. During each of his many hospital admissions he had one to three such seizures, with unconsciousness lasting from 5 to 40 minutes. With regard to respiratory symptomatology, he was first admitted six years before death with chills, fever, malaise, and cough and was discharged six days later with the diagnosis of acute upper respiratory infection. A year later he complained of dyspnea and orthopnea for the first time. A chest roentgenogram at that time revealed cardiac hypertrophy and findings consistent with pulmonary congestion and chronic bronchitis. An electrocardiogram was normal; however, five days after admission he began to have fibrillation and peripheral edema developed. He responded well to digitalis and diuretics. An electrocardiogram a year later was again normal.

Three years and two months before death he was admitted with a history of productive cough for six days, with dyspnea, nausea and vomiting, and left chest pain. He appeared acutely ill, with a temperature of 103 F, dyspnea, cyanosis, and a pulse rate of 136 per minute. The chest roentgenogram showed a cardiomegaly and pulmonary congestion. He recovered with sulfathiazole treatment, although cough and dyspnea lasted three weeks. He was next seen about two years later, with substernal pain, cough, and night sweats for about four days. He had had severe dyspnea on exertion for some time. His blood pressure was normal. There were rales in the right lung and bronchial breath sounds in the left. An electrocardiogram for the first time showed evidence of myocardial damage, with changes in the T-waves suggesting recent injury. He was again treated with sulfonamide drugs and was discharged with the diagnosis of acute respiratory infection and mild congestive failure. His last admission was three months before death, when he complained of acute precordial pain with nausea and vomiting, dyspnea, mild peripheral edema, and mild cyanosis. An electrocardiogram revealed old, but no recent, myocardial damage. He was treated on a cardiac regime and discharged 40 days later. Two months after discharge he was found dead in bed.

At necropsy the heart weighed 540 gm. The right ventricular myocardium was 0.9 cm. and the left 1.5 cm. thick. The heart valves were normal. The coronary arteries were all sclerotic. There were an old occlusion of the left descending coronary artery and a recent thrombus in the left circumflex artery. The right lung weighed 750 gm. and the left 880 gm. The lungs appeared voluminous, with glistening pleura, and were of a reddish color on section. No areas of recent or old consolidation were found. The liver weighed 1590 gm. and appeared normal. The spleen weighed 390 gm. and was deep-red on cut section. The brain was not examined.

Microscopically, the heart revealed severe myocardial fibrosis with large areas of old infarction. No recent infarction was found, probably because of the rapidity of death following the coronary thrombosis described above. There was a moderate diffuse sprinkling of siderophages through the lungs. Basophilia, thickening, and fragmentation of elastic tissue were seen in the alveolar walls and in the walls of small and medium-sized arteries. This elastica change was accompanied by a striking foreign-body-giant-cell reaction (Fig. 2). Many of the small arteries containing basophilic elastic fibers were crescentically enveloped for over 50% of their circumference by phagocytic giant cells. There was mild irregular emphysema, and considerable pulmonary fibrosis, characterized by a loose connective tissue meshwork.

Summary.—This 51-year-old man, with a long history of severe grand mal epilepsy, gave a five- to six-year history of pulmonary and cardiac symptoms. The pulmonary symptoms consisted of occasional bouts of illness, diagnosed as acute respiratory infections, and increasing dyspnea. The cardiac symptoms and anatomic findings were typical of severe coronary arteriosclerosis. He died of acute coronary-artery thrombosis. The lungs showed severe elastica disease, with sclerosing foreign-body response and fibrosis.

Case 12.—A 56-year-old white man, a cattle dealer, entered the hospital with dyspnea and weakness of one year's duration. He had been placed upon a strict cardiac regime five months previously by his local physician but remained symptomatic. He gave a 15-year history of gout, with attacks occurring about twice a year, and a 10-year history of hepatosplenomegaly, which had been diagnosed as Banti's disease. On admission, his heart, liver, and spleen were enlarged, and a 3+ ankle edema was present. The red blood cell count was 1,780,000, and hemoglobin was 5 gm. per 100 cc. A sternal-marrow aspiration specimen was very cellular, with many immature cells and mega-

karyocytes. The chest roentgenogram revealed "hazing" throughout the lung fields. The patient became febrile; rales were heard in the chest, and he died a few days after admission.

At necropsy, the peritoneum was seen to contain 500 ml. of yellow fluid. The heart weighed 425 gm. The right ventricular myocardium was 0.3 to 0.4 cm. thick. The left heart and all cardiac valves were normal. The right lung weighed 1320 and the left 950 gm. The cut surfaces were gray-tan in color, granular, and of a solid, liver-like consistency. The liver weighed 2850 gm. and was enlarged to the pelvic brim. Its cut surface was yellow-tan, with some blurring of architecture. The spleen weighed 1750 gm. and was a dark gray-purple color, firm, and reddish-purple on section. The bone marrow was red and firm.

Microscopically, the heart was normal. The lungs revealed marked edema and engorgement of alveolar walls with blood. There was a striking diffuse and nodular siderophagia. Focal areas of bronchopneumonia were present. Basophilia, thickening, and fragmentation of vascular elastic tissue were severe (Fig. 6, left), with tortuosity of vessels and irregularity of vascular contour. There was an apparent increase in the number of medium-caliber artery-capillary communications. A fibrovascular, spongy thickening of the alveolar septa with capillary ectasia was especially prominent in the atrial walls. There was some basophilia of the capillary loops on their luminal side, due to iron imbibition by reticular tissues. Elastica changes were severest in arteries but involved also veins, bronchial elastic tissue, and alveolar walls (Fig. 7). Giant cells, accumulated intramurally within larger arteries, had phagocytosed elastic tissue (Fig. 3). The altered elastic fibers gave the expected staining reactions. Rare bluish globular bodies were seen. A moderate diffuse fibrosis of alveolar walls was present. The liver was hyperemic and showed cloudy swelling. The spleen was moderately fibrotic, and areas of hematopoiesis were present. The bone marrow was extremely hyperplastic.

Summary.—A 56-year-old man gave a one-year history of increasing dyspnea, weakness, orthopnea, ankle edema, and marked anemia. Death was due to early bronchopneumonia superimposed upon a severe pulmonary elastica disease. The 10-year history of hepatosplenomegaly, anemia, and hyperplastic bone marrow corresponds to a refractory anemia with immature cellular marrow[2] and may have been incidental to the pulmonary disease.

Summary of Clinical Features

The over-all clinical picture that may be associated with the pulmonary elastica disease described in this study is briefly indicated in the Table. The observed age range of 24 to 73 years, with a mean of 53.5 years, is doubtless heavily weighted, since 11 of the 12 cases were from a veterans' hospital. The constant occurrence, alone or in combinations, of dyspnea and the frequency of cyanosis, hemoptysis, peripheral edema, febrile episodes, polycythemia, normal or abnormal blood pressure recordings, and the presence of other diseases, including severe grand mal epilepsy in two patients, are noted in the Table. The average duration of pulmonary symptoms was 6.7 years. The course of the pulmonary symptoms was in general fairly steady and progressive, rather than episodic. The concomitant occurrence of left heart disease in a number of the patients would, of course, greatly complicate diagnostic interpretation. The finding of a cor pulmonale in the absence of left heart disease should alert the clinician to the possibility that he is dealing with a pulmonary elastica disease.

Summary of Pathologic Findings

Grossly, the lungs were heavier than normal, with variable evidence of congestion, edema, emphysema, and fine diffuse fibrosis. These changes, when present, were distributed diffusely throughout the lungs. When the elastica changes were predominantly vascular, rather than interstitial, the gross findings were minimal.

Microscopically, one may see in the lungs, in severe cases, a marked basophilia, thickening, fragmentation, and sharp angulation

Synopsis of Twelve Autopsied Cases of Pulmonary Fibrosis and Giant-Cell Reaction Associated with Altered Elastic Tissue

Case	Age, Yr.	Duration of Pulmonary Symptoms, Yr.	Dyspnea	Cyanosis	Hemoptysis	Peripheral Edema	Febrile Episodes	Polycythemia	Blood Pressure	Cor Pulmonale	Heart Disease Other than Cor Pulmonale	Other Diseases of Pertinence	Severity of Pulmonary Elastica Changes	Degree of Siderophagia (Heart Failure Cells)
1	53	1	+	+	−	+	−	+	Normal	+	None	−	++++	+
2	24	4½	+	+	+	−	+	+	80/40	+	None	−	++	−
3	51	1-2	+	+	−	+	−	−	Normal	−	Syphilitic aortic valvulitis	−	++++	+
4	58	1	+	−	−	+	−	+	290/140	−	HCVD	−	++	+++
5	56	2	+	−	+	−	−	−	150/80	+	HCVD	−	++	++++
6	57	13	+	−	+	+	−	−	160/90	+	Mitral stenosis	Grand mal epilepsy	+++	+++
7	49	10	+	+	+	−	−	−	Normal	+	Mitral & aortic stenosis	−	++	++
8	73	5	+	−	+	+	−	−	220/112	+	HCVD	Diabetes	++	+
9	62	15	+	−	+	+	−	−	Normal	+	None	Marked emphysema	+	+
10	51	6	+	+	+	−	+	−	Normal	+	ASHD	Grand mal epilepsy	+++	++
11	52	21	+	+	+	+	−	+	Normal	+	Mitral stenosis	−	+	+++
12	56	1	+	−	−	−	−	−	Normal	−	None	Gout, refractory anemia	++++	++++

of vascular and interstitial elastic tissue fibers. The earliest vascular change would appear to be hyalination of vascular elastic tissue. This was seen in Cases 4 and 10. This is soon followed by thickening and reduplication of elastic fibers, with eccentric bulging and widening of the vessel wall. The smallest vessels may contain bland thrombi. In one of our cases (Case 2) both active and healed arteritis of a few small and medium-sized vessels could be demonstrated. No evidence of this arteritis, however, could be found in the lung biopsy specimen obtained about two years before death, approximately midway in the course of the patient's illness.

With further progression of the more characteristic, nonarteritic lesion of the vessels, the altered elastic tissue becomes intensely basophilic, due to imbibition of iron compounds. It is this change which immediately catches the eye on even a casual survey of lung sections from a severe case. The elastic fibers become brittle and fragment. A marked foreign-body reaction ensues. This may be due partly to an irritant action from large collections of iron compounds, and partly to the presence of fractured elastica fragments, or there may be other causes. Luminal obliteration of arteriolar vessels may sometimes be observed, but larger vessels usually appear distended, as though hung upon a skeleton of rigid elastic fibers. Intramural vascular extravasation of erythrocytes, suggesting minute dissection of vessels, may occasionally be observed. Both small and larger arteries appear tortuous, and an abruptness of transition occurs between small arteries and capillary vessels.

Interstitial changes in elastic tissue in this disease may be diffuse or focal and may take two forms. First, the altered elastic tissue associated with vessels often winds off into adjacent interstitium, retaining at the same time its marked basophilia.

Second, the interstitium itself may contain focal aggregates of foreign-body giant cells, from one to perhaps a dozen in number and grouped in relation to altered elastic tissue. These changes may be found involving atria, bronchiolar walls, intralobular septa, and subpleural tissues. The interstitial and vascular components may vary considerably in relation to each other, from the predominantly interstitial involvement, of Case 1, to the predominantly vascular involvement, of Case 3, to the approximately equal involvement of vasculature and interstitium, in Case 10. Bluish globular bodies having a laminated structure, and resembling Schaumann bodies, can usually be found on careful search. Sometimes these may form a striking adjunct to the basic lesion. They are found in and about giant cells. Asteroid bodies were observed in Case 1 only.

Besides the more specific elastica changes, one finds a diffuse fibrosis of alveolar walls and pulmonary septa. This is roughly proportional to the severity of the elastica injury. Sometimes the capillary channels in the lungs are engorged, bulge, and create the appearance of a capillary ectasia. Siderophages having both a diffuse and a nodular distribution are prominent in some cases and are minimally present or absent in others (Table). There is no constant relationship between the degree of siderophagia and the degree of basophilia of the elastic fibers in either vessels or interstitium. In areas where the siderophagia is prominent, the alveolar-lining cells often show cuboid metaplasia. Mononuclear-cell infiltration, edema, and fibrin deposition are absent or minimal, and the histopathologic picture seen in these cases does not suggest a basic inflammatory process or organizing pneumonitis.

The altered elastic tissue in both vessels and interstitium, and inside and outside giant cells, gives positive reactions with the orcein, resorcin-fuchsin, and Verhoeff's elastica stains. The basophilic elastic tissue gives a strongly positive reaction for iron. Microincineration reveals large amounts of iron in areas corresponding to elastic tissue in the lungs. Calcium can be shown to be absent with this technique insofar as elastic tissue is concerned. Reticulin, as demonstrated by Wilder's stain, is variable and would seem to depend upon the stage and degree of pulmonary fibrosis.

The frequency of cor pulmonale among our cases is 9 out of 12, as shown in the Table. Cor pulmonale is often marked, the right ventricular myocardium being over 1 cm. in thickness. Changes in the liver and, to a less degree, in the spleen, characteristic of right heart failure, are often present. Elastic tissue changes are found only in the lungs.

Comment

The absence of cardiac pathologic change other than cor pulmonale in 4 of the 12 cases reported in this study deserves special emphasis (Table). It is especially noteworthy that three of the four severest cases of pulmonary elastica disease occurred in the absence of any heart disease except cor pulmonale. The cor pulmonale must be regarded as secondary to, rather than causative of, the pulmonary changes. The elastica pathology, therefore, is not necessarily associated with, and certainly not caused by, chronic pulmonary congestion or left-sided heart failure but may occur as a primary pulmonary form.

We visualize the pathogenesis of this pulmonary elastica disease tentatively as follows: As a result of unexplained, and perhaps multiple, causes arteritis, allergic injury, metabolic or structural defect ?) the elastica undergoes peculiar changes, characterized by hyaline thickening, reduplication, and fragmentation. This renders it susceptible to impregnation by iron compounds. This impregnation depends upon (*a*) the receptivity of the elastic tissue for iron and (*b*) the concentration of locally available iron. In the presence of excessive local concentration of iron, such as occurs in prolonged passive congestion, impreg-

nation of the elastica may take place before the primary elastica changes are very far advanced. However, if the elastic tissue is sufficiently altered, it may adsorb iron even in the absence of a high local concentration of iron. This hypothesis assumes a developing derangement in the metabolism of elastic tissue to account for those changes observed in the absence of primary cardiac pathology, and also seeks to explain the association with left-sided heart disease observed in a number of cases. Finally, the iron-impregnated, fragmented elastic tissue acts as an irritant and locally traumatic substance, which provokes a sclerosing foreign-body reaction in the lungs, with resultant pulmonary insufficiency and cor pulmonale.

It is pertinent now to enter into some discussion of disease states in which elastica changes occur that are similar to those we have described, or in which one might wonder whether they occur. Basophilic degeneration of connective tissue with fibrosis and giant-cell response is at once suggestive of the so-called Gamna-Gandy body,† or siderotic nodule. This nodule is described in the spleen in fibrocongestive splenomegaly, in sickle-cell disease, and in certain cases of hemochromatosis.[14] In the spleen these nodules are related to local perifollicular hemorrhages, with the long-term build-up of hemosiderin deposits. In our experience collagenous fibers would appear to be more especially affected by iron impregnation at this site than are elastic fibers. We believe that the connective-tissue portion of the siderotic nodule is more in the nature of "elastotic" degeneration of collagenous scar tissue, in the sense used by Gillman and associates[11] than a fundamentally elastica process. While this seems generally true, it should be noted that the elastica is also affected to some degree in such spleens.[9] Gamna-Gandy bodies have not been reported elsewhere than in the spleen, to our knowledge. We have observed this type of reaction, however, in the lymph nodes of a case of hemochromatosis. It may be concluded that the pulmonary elastica process described in this paper is morphologically similar to, but not identical with, the Gamna-Gandy body. The occurrence of the process in lungs in which there is no evidence of excessive hemosiderin deposition, except as may be directly attached to the elastic fibers, is in contrast to the classical concept of the pathogenesis of Gamna-Gandy body formation.

The entity known as "idiopathic pulmonary hemosiderosis," or "essential brown induration of the lungs," is characterized clinically by episodic attacks of fatigue, cyanosis, pallor, dyspnea, anemia, and cough, with traces of blood in the sputum. With a few exceptions,‡ this chronic, usually fatal, disease is limited to young children in the vicinity of 5 years of age. Thirty cases had been described up to 1954.[26] The most comprehensive review is that of Wyllie and associates.[33] Histologically the lungs are described as showing extensive intra-alveolar hemorrhage, nodular siderophagia, cuboid metaplasia of alveolar lining cells, pulmonary fibrosis, swollen basophilic, often reduplicated, septal and vascular elastic tissue, and phagocytosis of altered elastic fibers by foreign-body giant cells.§ None of the authors who have studied these cases saw fit to call the elastica changes Gamna-Gandy formation, despite the superficial similarities we have pointed out. A number of speculations are on record regarding the etiology of idiopathic pulmonary hemosiderosis. Some cases[21] were thought to show grossly deficient pulmonary elastic tissue. The theory of a structural defect in the lungs was advanced in the original description by Ceelen[5] and supported by Borsos-Nachtnebel.[3] Glanzmann and Walthard[12] felt that a circulatory disorder of the lungs due to defective elastic tissue might be etiologic. McLetchie and Colpitts[21] considered that all of the pulmonary changes could be explained on the

† References 9, 17.

‡ References 3, 8, 21, 25.

§ References 7, 26, 33.

basis of anoxemia, a primary unexplained lung condition producing defective aeration. The fact that the Gamna-Gandy process occurs in disorders where defective oxygenation and local build-up of hemosiderin are present might lend some indirect support to this last idea, if one admits of the comparison. Owing to the good response following splenectomy of a 6-year-old male child whose disease had previously been diagnosed by lung biopsy, Steiner [26] considered the disease to be immunoallergic in nature, the lung being the shock organ. Other instances of striking amelioration or cure following splenectomy are on record.[6]

Only three cases of idiopathic pulmonary hemosiderosis confirmed histologically have been reported in adults to our knowledge. The ages were 16,[8] 20,[5] and 44.[25] The disease was fatal in a few years in the first two instances and in nine years in the latter. Virchow [29] mentioned having seen a peculiar type of severe brown induration of the lungs of young women, occurring in the absence of heart disease.

The possible relation of the pulmonary elastica changes described in this paper to so-called idiopathic pulmonary hemosiderosis is speculative. Certain histopathologic similarities are obvious. The chief histopathologic difference centers about the degree of pulmonary alveolar hemorrhage and siderophagia. This feature is always marked in idiopathic pulmonary hemosiderosis but was quite variable and sometimes minimal to absent to our cases (Table). From a clinical standpoint, our cases showed a chronic progressive course, whereas idiopathic pulmonary hemosiderosis generally presents as episodic bouts of fever, cough, and pulmonary hemorrhage, with marked anemia. Such dissimilarities, however, might be explained on the basis of age difference, the mean age at time of death in our cases being 53.5 years. McLetchie and Colpitts [21] pointed out that of 24 recorded cases of idiopathic pulmonary hemosiderosis, 16 are the work of five groups of investigators, leading them to assume that the diagnosis is often overlooked. We suspect that a similar line of reasoning might apply to the cases in this study.

Basophilia of pulmonary elastic tissue has been mentioned as occurring in the lungs in mitral stenosis,‖ and in severe left ventricular failure due to other cause.[20] Lendrum [20] found nodular siderophagia in the lungs of 26 of 33 autopsied patients with mitral stenosis. This included all cases in which there were recognizable focal deposits of hemosiderin, irrespective of degree. An unspecified number (all but one of his pertinent photomicrographs are from the same case) revealed changes in elastic tissue similar to those described in this report. Lendrum does not make clear to what degree iron stains were required to show the alteration of elastic tissue, and to what degree a basophilia with hemalum alone was present. In his series the changes were always focal, and the pulmonary tissue between the nodular areas of siderophagia was interpreted to be not far from normal. Lendrum, Scott, and Park [20] felt that this type of pulmonary hemosiderosis, including the elastica changes, was due purely to the heart disease and denied the possible role of "rheumatic pneumonia." Weir and associates,[31] despite striking pathological and radiological evidence of pulmonary hemosiderosis, did not describe any elastica changes in the lungs of their case beyond "a bluish imbibition of the stroma about the hemosiderotic areas" with iron stains. In an analysis of 10 cases of rigid mitral stenosis associated with dyspnea, cyanosis, and occasionally frothy hemoptysis, Parker and Weiss [23] described no specific elastica changes, and in their main illustrative case elastic tissue was specifically said to be normal. More recently, Taylor and Strong [28] studied the pulmonary changes in 45 autopsied cases of mitral stenosis. Among this number, 14 had diffuse, 8 mild focal, and 11 marked focal (nodular) siderophagia. These nodules were sometimes 0.4 to 3 mm. in size. Iron impregnation of

‖ References 19, 20, 28.

septal connective tissue, including elastica, could be demonstrated with Perl's stain, but no mention is made of basophilia with the hematoxylin stain. No giant-cell reaction, such as that described and illustrated by Lendrum,[19] was reported.

It seems apparent that pulmonary connective- and elastic-tissue changes related to direct impregnation by iron may occur in the occasional case of mitral stenosis and other forms of left-sided heart failure. However, with the exception of Lendrum's case or cases, these changes are inconstant and mild. Our own observations, indicating that iron impregnation of elastic tissue and giant-cell reaction may exist to an advanced degree when pulmonary siderophagia is minimal or absent, and in the absence of left-sided heart disease, suggest that further explanation beyond the simple local availability of iron must be sought to explain these lesions.

Gouley[15] states that the pulmonary changes in late rheumatic heart disease, such as mitral stenosis, are not wholly due to congestive failure but are in major part the result of recurring inflammation. He recognizes acute, subacute, and chronic rheumatic pneumonopathy. In the acute form, he describes an arteritis and, besides this, dissolution of alveolar elastica into small shreds and dots. In the subacute phase, a beginning interstitial fibrosis and early regeneration of elastic tissue is described. In the chroinc stage, special stains are said to reveal a marked hyperplasia of elastic tissue, most prominent in the thickened alveolar walls. Gouley[15] designates this process as "pulmonary elastosis."

A rather extensive and inconclusive literature has accumulated with regard to "rheumatic pneumonitis." This literature is generally confined to the more acute or subacute forms, so that it is only indirectly pertinent to the problem at hand. Muirhead and Haley[22] reviewed the literature up to 1947 and reported a case showing features of subacute and chronic "rheumatic pneumonitis." They did not discuss elastica changes in their case, although cognizant of Gouley's contributions.[15] Except for the arteritis found at autopsy in Case 2, our cases did not show features that would suggest rheumatic involvement of the lungs. However, this question is difficult to resolve, as the histopathology of chronic "rheumatic pneumonitis" is nonspecific and poorly delineated.

With reference to Braunstein's[4] comments on periarteritis nodosa limited to the pulmonary circulation, one might wonder if in the present instances we could be dealing with the end-stage of a peculiar pulmonary arteritis. In our Case 2, and in the cases of idiopathic pulmonary hemosiderosis reported by Steiner[26] and by Russi and Wingo,[25] lung biopsy performed for diagnostic purposes during the active downhill course of the respective patients failed to show any evidence of an arteritis. In Russi's[25] case an entire lobe was available for study. There is some indication that pulmonary hypertension may itself be responsible for an arteritis.[4] We should be more inclined to accept this explanation for the observation of an arteritis at autopsy in our Case 2 than to ascribe an arteritis as etiologic for the entire series.

Degeneration of vascular elastic tissue is well recognized as a feature of pseudoxanthoma elasticum.[27] These degenerated fibers imbibe calcium. In Balzer's original case[1] elastica degeneration between pulmonary alveoli was found at autopsy. Wolff and associates[32] reported the case of a 14-year-old boy with pseudoxanthoma elasticum whose chest x-ray showed miliary mottling of the left lung field. The authors attributed this finding to multiple small intra-alveolar hemorrhages, due to degeneration of elastic tissue of the lung septa. A structural defect of pulmonary elastic tissue is thus called to mind, which conceivably might produce changes resembling those described here.

It may be concisely stated by way of exclusion that, on review of pertinent material, we feel that the cases described herein present no convincing features of

the Hamman-Rich type of diffuse interstitial pulmonary fibrosis,¶ or of the pulmonary manifestations of scleroderma,[10] or of "rheumatoid disease with pulmonary manifestations."[24]

Conclusion.—The pulmonary change seen in our 12 cases is basically related either to an idiopathic structural defect in elastic tissue or to acquired damage of elastic tissue by immunologic, metabolic, or perhaps inflammatory ("rheumatic pneumonitis") means. The pulmonary elastic tissue is the target organ of some type of injurious process. More than one type of etiology is entirely possible. Among previously described entities that have to do with pulmonary elastic tissue, that designated as "idiopathic pulmonary hemosiderosis," in most instances a disease of childhood, seems most closely akin to the cases of this report. Heart disease seems not to be a primary cause, although it may increase the amount of iron locally available in the lungs. Once sufficiently in progress, the pulmonary changes are to some degree self-perpetuating. The sharp and fractured elastic fibers appear to act in the manner of inert foreign material and to provoke a marked foreign-body reaction with pulmonary fibrosis.

Summary

The clinicopathologic findings in 12 autopsied cases of a peculiar pulmonary elastica disease are presented. Clinically these cases were characterized by a fairly progressive course, lasting from 1 to 21 years (average, 6.7 years), with symptoms of dyspnea, cyanosis, frothy hemoptysis, and cor pulmonale. Left-sided heart disease, including mitral stenosis, aortic stenosis, hypertensive heart disease, arteriosclerotic heart disease, and syphilic valvulitis, was concomitant in eight cases and absent in four cases. Histologically, the pulmonary elastic tissue showed marked fragmentation, reduplication, thickening, and intense basophilia. These elastica changes provoked an intense sclerosing foreign-body-giant-cell reaction and pulmonary fibrosis sufficient to cause death directly from pulmonary failure. The pertinent literature, having to do with pulmonary elastica disease of various types, is discussed. This includes Ceelen's idiopathic pulmonary hemosiderosis, the pulmonary changes in mitral stenosis, rheumatic pneumonitis, and pseudoxanthoma elasticum, as well as others. Injured pulmonary elastic tissue may act as a foreign body or sequestrum and produce a progressive "pneumoconiosis."

¶ References 13, 16.

REFERENCES

1. Balzer, F.: Recherches sur les caracteres anatomiques du xanthelasma, Arch. physiol. norm. et path. (Series 3) 4:65, 1884.

2. Bomford, R. R., and Rhoades, C. P.: Refractory Anemia: I. Clinical and Pathological Aspects, Quart. J. Med. 10:175, 1941.

3. Borsos-Nachtnebel, O.: Zur Pathologie der Lungen-hämosiderose, Zentralbl. allg. Path. u. path. Anat. 79:174, 1942.

4. Braunstein, H.: Periarteritis Nodosa Limited to the Pulmonary Circulation, Am. J. Path. 31: 837, 1955.

5. Ceelen, W., in Handbuch der speziellen pathologischen Anatomie und Histologie, edited by F. Henke and O. Lubarsch, Berlin, Springer-Verlag, 1931, Bd. III, T. 3, p. 20.

6. Cordeiro, M.: Un cas d'hémosidérose pulmonaire idiopathique guéri par splenectomie, Helvet. paediat. acta 7:501, 1952.

7. Delage, J.: Essential Pulmonary Hemosiderosis, Acta med. scandinav. 145:382, 1953.

8. Ellman, P., and Gee, A.: Pulmonary hæmosiderosis, Brit. M. J. 2:384, 1951.

9. Gamna, C.: Contributo alla conoscenza delle splenomegalie croniche primitive: Splenogranulomatosi siderotica, Haematologica 4:129, 1923.

10. Gentzowa, S.: Cystic and Compact Pulmonary Sclerosis in Progressive Scleroderma, Arch. Path. 40:99, 1945.

11. Gillman, T.; Penn, J.; Bronks, D., and Roux, M.: Abnormal Elastic Fibers, A. M. A. Arch. Path. 59:733, 1955.

12. Glanzmann, E., and Walthard, B.: Idiopathische progressive braune Lungeninduration im Kindesalter mit hereditärer Hämoptyse, Monatsschr. Kinderh. 88:1, 1941.

13. Golden, A., and Bronk, T. B.: Diffuse Interstitial Fibrosis of Lungs: Form of Diffuse Interstitial Angiosis and Reticulosis of Lungs, A. M. A. Arch. Int. Med. 92:606, 1953.

14. Goldish, R. J., and Aufderheide, A. C.: Secondary Hemochromatosis: II. Report of a Case

Not Attributable to Blood Transfusions, Blood 8: 837, 1953.

15. Gouley, B. A.: Evolution of the Parenchymal Lung Lesions in Rheumatic Fever and Their Relationship to Mitral Stenosis and Passive Congestion, Am. J. M. Sc. 196:1, 1938.

16. Hamman, L., and Rich, A. R.: Acute Diffuse Interstitial Fibrosis of the Lungs, Bull. Johns Hopkins Hosp. 74:177, 1944.

17. Hu, C. H.; Reimann, H. A., and Kurotchkin, T. G.: Filaments in Siderotic Nodules of Spleens in Cases of Splenomegaly of Unknown Origin, Proc. Soc. Exper. Biol. & Med. 26:413, 1929.

18. Kaufman, H. E., and Adams, E. C.: Water-Soluble Chelates in Histochemical Staining, Science 120:723, 1954.

19. Lendrum, A. C.: Pulmonary Hemosiderosis of Cardiac Origin, J. Path. & Bact. 62:555, 1950.

20. Lendrum, A. C.; Scott, L. D. W., and Park, S. D. S.: Pulmonary Changes Due to Cardiac Disease with Special Reference to Hemosiderosis, Quart. J. Med. (new series) 19:249, 1950.

21. McLetchie, N. G. B., and Colpitts, G.: Essential Brown Induration of the Lungs (Idiopathic Pulmonary Haemosiderosis), Canad. M. A. J. 61:129, 1949.

22. Muirhead, E. E., and Haley, A. E.: Rheumatic Pneumonitis, Arch. Int. Med. 80:328, 1947.

23. Parker, F., and Weiss, S.: The Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis, Am. J. Path. 12:573, 1936.

24. Rubin, E. H.: Pulmonary Lesions in "Rheumatoid Disease" with Remarks on Diffuse Interstitial Pulmonary Fibrosis, Am. J. Med. 19: 569, 1955.

25. Russi, S., and Wingo, C. F.: Idiopathic Pulmonary Hemosiderosis, Am. J. Path. 32:611, 1956.

26. Steiner, B.: Essential Pulmonary Haemosiderosis as an Immuno-Haematological Problem, Arch. Dis. Childhood 29:391, 1954.

27. Szymanski, F. J., and Caro, M. C.: Pseudoxanthoma Elasticum: Review of Its Relationship to Internal Diseases and Report of an Unusual Case, A. M. A. Arch. Path. 71:184, 1955.

28. Taylor, H. E., and Strong, G. F.: Pulmonary Hemosiderosis in Mitral Stenosis, Ann. Int. Med. 42:26, 1955.

29. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1864, Bd. 2, p. 470.

30. Walford, R. L., and Kaplan, L.: Endogenous "Pneumoconiosis" Associated with Altered Elastic Tissue, Am. J. Path. 32:611, 1956.

31. Weir, J. A.; Piccoli, A. J.; Greene, D. G., and Greene, C. W.: Mitral Stenosis with Exertional Cyanosis and Pulmonary Hemosiderosis, Circulation 6:868, 1952.

32. Wolff, H. H.; Stokes, J., and Schlesinger, B.: Vascular Abnormalities Associated with Pseudoxanthoma Elasticum, Arch. Dis. Childhood 27:82, 1952.

33. Wyllie, W. G.; Sheldon, W.; Bodian, M., and Barlow, A.: Idiopathic Pulmonary Haemosiderosis (Essential Brown Induration of the Lungs), Quart. J. Med. 17:25, 1948.

The Lesion of Morton's Metatarsalgia (Morton's Toe)

THOMAS M. SCOTTI, M.D., Coral Gables, Fla.

Introduction

The purpose of this paper is to emphasize the nature and pathogenesis of the lesion which is associated with a fairly common syndrome referred to as "Morton's toe" or "Morton's metatarsalgia." Generally, the surgeon is the one to whom a patient with this disease is referred, for surgical treatment is curative in practically all cases. Yet the general practitioner should be familiar with its characteristic clinical features, as he is often the first to be consulted by the patient. Not uncommonly a patient first consults a chiropodist for this ailment. The lesion is so distinctive that the pathologist should have no trouble in recognizing its features in the specimen submitted to the laboratory.

Clinically, the syndrome is seen oftener in women than in men and is characterized by neuralgic pain in the foot, usually beneath the heads of the third and fourth metatarsals, less commonly beneath the second or third metatarsal head. The pain usually commences after excessive walking or standing, and in a few instances it originates after slight trauma, such as stepping on a stone. The pain is often accompanied by a localized area of tenderness and may extend from the sole into one of the digits, particularly the fourth. Occasionally, it may extend up the posterior aspect of the leg as far as the hip.[1] Characteristically, the patient obtains relief, with few exceptions, by resting and by removal of the shoe. Paresthesias and even lack of sensation into the affected toes has been observed in some cases. In an occasional instance one can palpate a mass between the third and fourth metatarsals. Rarely, the mass may be so large as to cause separation of the third and fourth metatarsals and toes as seen in the roentgenogram, and may even cause a swelling on the dorsum of the foot when the patient is standing.[2] Generally, however, there is no specific change observed in roentgenograms. Sometimes, firm deep pressure over the localized tender spot reproduces the radiating pain and paresthesias distally into the toes.[1] In the majority of cases the disease is unilateral, but in a significant number it is bilateral. Signs of inflammation are not evident. The symptoms of the disease are associated with a particular lesion of the plantar digital nerve, commonly referred to as "neuroma" or "neuritis," the nature of which will be discussed later.

In the present article an historical summary of the subject will be presented, followed by a review of my own material. Clinical and pathologic features and the pathogenesis of this entity will be discussed.

Historical Summary

It is not intended here to review every article on the subject; rather, the purpose is to refer to certain ones which adequately cover the development of our knowledge concerning Morton's metatarsalgia. The author who is usually cited in the medical literature as being the first to describe this syndrome, in 1876, is Thomas G. Morton, after whom the entity is named. In his report [3] he presented patients with "a peculiar and painful affection of the fourth metatarsophalangeal articulation," which, as far as he was aware, had not previously been de-

Submitted for publication July 16, 1956.

Associate Professor of Pathology, University of Miami School of Medicine, and Associate Pathologist, Jackson Memorial Hospital.

Department of Pathology, University of Miami School of Medicine, Coral Gables, Fla., and Jackson Memorial Hospital, Miami, Fla.

scribed. However, in the chiropodical literature [4] credit for the original description of this type of metatarsalgia is given to Lewis Durlacher, of England, surgeon chiropodist to the Queen. In 1845, Durlacher [5] wrote: Another form of neuralgic affection occasionally attacks the plantar nerve on the sole of the foot, between the third and fourth metatarsal bones, but nearest to the third, and close to the articulation with the phalanx. The spot where the pain is experienced can at all times be exactly covered by the finger. The pain, which cannot be produced by the mere pressure of the finger, becomes very severe whilst walking, or whenever the foot is put to the ground . . . I cannot assign any cause for its occurrence. Relief can only be afforded by the application of lateral compression, a strip of plaster about an inch wide being drawn tightly over the foot and round the sole. I believe this application acts by drawing the metatarsal bones closer, and thus affording protection to the affected nerve, which, when the parts are capable of expansion, is more exposed to pressure.

T. G. Morton,[3] in his study of the anatomy of the metatarsophalangeal region, concluded that "to the peculiar position which the fourth metatarsophalangeal articulation bears to that of the fifth, the great mobility of the fifth metatarsal which by lateral pressure is brought into contact with the fourth, and lastly, the proximity of the digital branches of the external plantar nerve, which are, under certain circumstances, liable to be bruised by, or pinched between the fourth and the fifth metatarsals, may be ascribed the neuralgia in this region." The operative treatment he recommended was removal of the joint of the fourth toe and the surrounding soft parts, including the nerves distributed about the joint. No evidence of disease was found in the parts removed. It is worthy to note that in the clinical evaluation of the first patient of his series he considered "either a neuroma or some nerve hypertrophy" as the cause of the metatarsalgia. This patient was not subjected to operation. He observed "that the affection, which has been seen more frequently in females, may be attributed not only to the greater delicacy and pliability of the female foot, as compared with the male foot, but perhaps in a measure to the prevailing custom, especially with fashionable women, of wearing tight and very narrow shoes." He refers to several instances where this neuralgia followed an injury.

It is an interesting fact that two other Mortons have contributed to the literature on this form of metatarsalgia. One of these was Thomas S. K. Morton,[6] who in 1892 confirmed the views of T. G. Morton and presented his own experiences with this entity. Most of the authors at about this time paid much attention to the use of conservative measures of therapy, such as fitting the patient with special shoes, but in cases of intractable pain, amputation of the toe or resection of the metatarsophalangeal joint was recommended. A different approach to therapy was presented by Hoadley in 1893, which is similar to the present-day treatment, but which for some reason was not adopted for many years. Hoadley (cited by Bickel and Dockerty [1] and Ringertz and Unander-Scharin [7]) in one of his patients resected a small neuroma of the digital branch of the lateral plantar nerve to the fourth toe and obtained "a prompt and perfect cure."

The third Morton, Dudley J., is responsible for a different interpretation of the pathogenesis of Morton's toe.[8] In 1935 he described metatarsalgia in cases with a short first metatarsal, a hypermobile first metatarsal segment, and a posterior displacement of the sesamoids. He believed that the stresses placed on the foot resulting from these changes lead to compensatory hypertrophy of the second metatarsal bone and traumatic arthritis with effusion of the second tarsometatarsal joint. He did not regard the pinching of the digital nerves between the heads of the metatarsal bones as the cause for metatarsalgia, as did T. G. Morton; but he suggested that the cause was congestion and irritability of the medial plantar nerve as it passes the affected second tarsometatarsal joint. As a result of this work, some writers [9] limit the concept of "Morton's syndrome" to metatarsalgia associated with a short first metatarsal and the other abnormalities described by D. J.

Morton. However, it is generally observed that patients with the typical symptom complex of Morton's toe as described in the present report do not have these associated skeletal abnormalities of the foot.

It was not until 1940 that the pathologic basis for the symptoms of this condition was established and impetus was given to the surgical treatment of Morton's metatarsalgia. This was done by Betts,[10] when he reported a series of 19 patients in whom neurectomy was performed through a longitudinal incision between the heads of the third and fourth metatarsals. In each case the fourth plantar digital nerve was affected. "In all cases the enlargement of the nerve has been obvious; in two the neuroma was as large as a pea, with a well defined bursal sac around it. Examination of a microscopic section revealed a great increase in the fibrous tissue element of the nerve." Resection gave relief from the neuralgic pain.

Betts offered an explanation of why the fourth plantar digital nerve "is subject to this neuritis." He noted that the fourth digital nerve is the only one which is of double origin, being formed by the medial plantar and a communicating branch from the lateral plantar, each coming around from opposite sides of the belly of the flexor brevis digitorum, where they unite. A few centimeters distally, the nerve divides to pass to the adjacent sides of the third and fourth toes. As a result of this double origin, the nerve is thicker and more fibrous than the other digital nerves, and this thicker part lies directly on the very firm transverse ligament. As a result of the contraction of the flexor brevis digitorum, the nerve is anchored at its point of origin from the two roots. When the toes are dorsiflexed, as in walking, this nerve is stretched around the unyielding transverse ligament, while the other plantar digital nerves slide easily longitudinally. As Betts states, "the neuritis probably arises in the first place from minor trauma, the head of the fourth metatarsal taking most of the weight on the outer side and being the part of the tread most exposed to such injuries. Once the nerve is swollen from neuritis a vicious circle is set up and the daily irritation is sufficient to keep it up." This explanation seemed quite plausible to most investigators, but, as Bickel and Dockerty observed, sometimes the double origin of the fourth plantar digital nerve is lacking, and "plantar neuromas" are found on the other digital nerves in some cases.

McElvenny,[11] working without knowledge of Betts' work, published his results in the management of 12 patients with Morton's metatarsalgia. He found that the condition was caused by a tumor involving the lateral branch of the medial plantar nerve, which he removed through a web-splitting incision. In his opinion, "Morton's toe is definitely a condition requiring surgery and permanent cure is gained by resection of the tumor." He stated that specimens of his series which were studied microscopically appeared to be either "neurofibromata" or "angioneuromata." He did not give a detailed description of the lesions, nor did he include photomicrographs in his report, so that it is not possible to determine the histologic basis for his interpretation.

The prevailing interpretation of the nature of the nerve lesion is that it represents a form of neural degeneration associated with fibrosis. It is necessary to mention only several of the reports which emphasize this. King [12] suggested the term "sclerosing neuroma" to describe the lesion, differentiating it from the ordinary amputation or traumatic neuroma. He did not consider it a true neoplasm, as is a neurofibroma or a neurinoma, but was of the opinion that it was a type of reactive hyperplasia with sclerosing and degenerative changes. He considered most neuromas as being analogous to keloids and regarded some long-continued traumatic factor as probably partly responsible for the characteristic appearance seen in the lesion of Morton's metatarsalgia. Bickel and Dockerty spoke of degenerative and proliferative nerve changes with tumefacient perineural fibrosis. They noted neural and perineural edema as well. Winkler, Feltner, and Kimmelstiel [13] did not

observe any active proliferation of either nerve or connective tissue. They thought that the lesion was purely degenerative, with resultant deposition of hyaline and collagenous material. Nissen [2] found degeneration of the plantar digital nerve, variable in degree, associated with a marked increase of epineural connective tissue. In addition, he observed several degenerative changes in the plantar digital artery: disruption of the arterial wall, thrombosis, and incomplete recanalization. He was of the opinion that the nerve changes were secondary to the arterial degeneration, that it was ischemic in nature, and he referred to the lesion as "plantar digital neuritis."

Mulder,[14] in 1951, observed that after the neuroma was carefully removed by gentle dissection, it was found to be adherent to the intermetatarsal bursa, intimately connected with the plantar wall of the bursa, so that it could not be removed without opening the bursa. The bursa was enlarged, with evidence of "frequent damage to its fibrous walls in the form of thickening and formation of irregular fibrous bands and layers." These observations suggested to him "that the neuroma is caused mechanically by repeated pinching of the plantar nerve between the metatarsal heads during the abnormal movements associated with weak transverse arches." He felt that "the plantar digital artery may also be caught and thereby included in the tumor." Thus, the writer "returns to Morton's original opinion, with the qualification—in agreement with most authors—that it is not the 4-5 but the 3-4, and sometimes the 2-3, interspace where the pinching takes place."

Later, Nissen [15] stated that Mulder's theory "merits careful consideration" and that surgeons should pay more attention to the intermetatarsophalangeal bursae. But he believed that adherence of the neuroma to the bursa, as described by Mulder, was a late occurrence. In his own experience, in the early acute cases, sometimes coming to operation within one or two months from the onset of pain, the nerve was not visibly thickened and was not adherent either to the ligament or to the bursa.

When a series of "young" specimens, consisting of digital nerve *and* vessels resected together, is arranged in the order of duration of symptoms up to twelve months, the progression of naked-eye changes from vascular and perivascular to neural and perineural is so continuous that the development of a "neuroma" and its tendency to bulge into the bursa appear to be a secondary phenomenon of no primary etiologic significance.

Ringertz and Unander-Scharin,[7] in addition to studying the anatomic changes in the resected plantar digital nerves and interdigital arteries of 18 cases of Morton's toe, also reviewed control material obtained at autopsy from patients who had no symptoms of Morton's metatarsalgia. In the surgically resected material they observed perineural fibrosis, "endarteritis" of the interdigital arteries, endoneural edema, and demyelination of the nerves. In the autopsy control specimens, they noted that perineural fibrosis and "endarteritis" occurred with the same frequency as in the patients with Morton's toe, but that intraneural edema and demyelination were considerably less frequent in the control material. However, fibrosis was not as marked in the control material as in some cases of Morton's metatarsalgia, nor was there any parellelism between the degree of fibrosis and the duration of severity of the symptoms, as suggested by Bickel and Dockerty [1] and Nissen.[15]

In view of these findings, the authors do not fully accept the theory proposed by Nissen that occurrence of this disease depends on "primary endarteritis" of the digital artery. The authors conclude that the "endarteritis-fibrosis complex" is so common in the interdigital neurovascular trunk of the foot, especially in patients over 40 years of age, that they wonder whether it may not all be physiologic (weight-bearing?). They further state that some special factors, so far unknown and possibly related to "endarteritis" or fibrosis, must be presumed for the appearance of the pain complex, and that the high incidence of intraneural edema and demyelination in

cases of Morton's metatarsalgia may provide a clue to further investigation of the true pathogenesis.

Present Material

This study is concerned with a review of the clinical findings and the surgically resected material of 17 patients who presented characteristic symptoms of Morton's metatarsalgia. It is interesting that three of these patients were first seen by a chiropodist who made the correct diagnosis. After the diagnosis was substantiated by surgical removal of the lesion, he included these cases in a report for the chiropodical literature.[4] In these three cases I obtained the gross specimens some years ago, while I was on the staff of the Medical College of Virginia. From these, microscopic sections stained with hematoxylin and eosin, Masson's trichrome method for connective tissue, and Bodian's silver technique for nerve fibers were studied. In two other cases, obtained from the files of Jackson Memorial Hospital, sections stained by the hematoxylin-eosin method were studied. The other 12 cases were obtained from the files of the Armed Forces Institute of Pathology. In one of these, only a microscopic section stained by the hematoxylin-eosin method was available. In the other 11 cases, sections were prepared from paraffin blocks of formalin-fixed tissue and stained by the following methods: hematoxylin and eosin; Masson's trichrome stain for connective tissue; Bodian's silver technique for nerve fibers; periodic acid-Schiff method; toluidine blue; Verhoeff's elastic stain with Van Gieson counterstain; Weigert's fibrin stain, and crystal violet for amyloid.

Clinical Features.—Of the 17 patients, 10 were women; 7 were men. All were white. The ages of the patients varied from 20 to 55 years: 20-29, three; 30-39, six; 40-49, four; 50-59, two; age not recorded, two. In only 1 of the 17 cases was the lesion bilateral. In all the others one foot was affected, usually the right (i. e., in 11 cases). The duration of symptoms was a few weeks in one patient, and in the others it varied from 3 months to as long as 10 years.

The common complaint in all of the patients was pain in the foot under the metatarsal arch, and in practically all cases at a point between the heads of the third and fourth metatarsals, while in one patient it was felt in the region of the head of the third metatarsal. The pain was characterized as "discomfort" or "a sensation of something there" in a few instances, but most frequently it was described as "crampy," "severe," or "excruciating." The pain was observed particularly during some form of activity, such as walking; and it sometimes was relieved after rest and when the shoe was removed. In one case, a throbbing sensation was experienced at night, and only partial or incomplete relief was obtained by use of shoe supports. Tenderness on the sole over the affected site was common. In a third of the cases there were associated symptoms, such as "numbness," "tingling," "burning," or "hyperesthesia to pinprick" between the third and the fourth toe or along the fourth toe. In two cases digital pressure on the sole, at the affected site, caused pain. In one it gave rise to shooting pains radiating into the toes, and in the other it reduplicated the pain the patient experienced while walking. In one case a roentgenogram showed a separation of the third and fourth toes with no apparent abnormality.

In all patients, definitive therapy was neurectomy, following, in some of the cases, a trial of conservative measures, such as use of arch supports or special shoes. In practically all the patients the fourth plantar digital nerve was affected. In one patient the third was involved. In this case the surgeon also observed "arthritic changes" of the third metatarsophalangeal joint and a bony spur of the head of the third metatarsal. The proximal half of the proximal phalanx of the third toe and the bony spur were also excised. The relief that follows surgical removal of the affected nerve in this condition is emphasized by the one patient of this series who had bilateral disease. The patient received complete relief of foot symptoms after neurectomy, although some anesthesia appeared between the third and fourth toes (an expected development), which did not disturb the patient. Six months later she developed symptoms of Morton's metatarsalgia in the opposite foot and requested surgical relief, which was obtained following another neurectomy. Signs

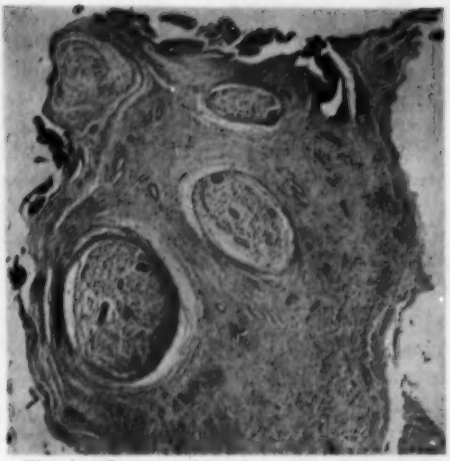


Fig. 1.—Cross section of a neuroma in a case of Morton's metatarsalgia. Note (1) interfascicular fibrosis with increased vascularization and separation of nerve bundles; (2) fibrous thickening of perineurium; (3) intrafascicular edema, some demyelination, and loss of nerve fibrils; (4) thickening and hyalinization of intrafascicular arterioles; (5) fibrin on the surface lining the wall of a bursa. Hematoxylin and eosin stain; reduced to 59% of mag. × 37.

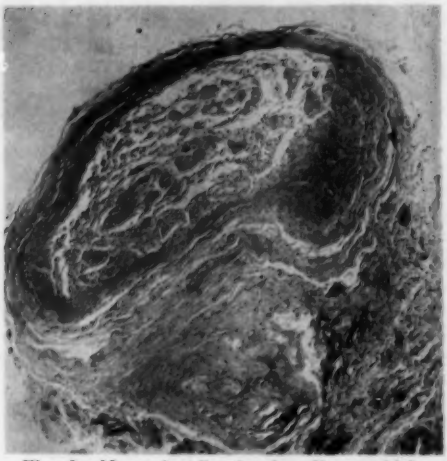


Fig. 2.—Nerve bundle showing fibrous thickening and hyalinization of perineurium with formation of a hyaline fibrous nodule. Intrafascicular edema and neural degeneratoin are pronounced. The loss of nerve fibrils causes "washed-out" appearance of nerve bundle. Areas of fibrosis with hyalinization and hyaline thickening of arterioles within the bundle are observed. Hematoxylin and eosin stain; reduced to 59% of mag. × 63.

of inflammation were not evident externally in the feet of any one of the patients. In the patient with involvement of the third plantar digital nerve and the associated bony spur, a large callosity was noted over the third metatarsal head.

Pathologic Features.—The gross specimen was available in only 3 of the 17 cases. In each of these the specimen consisted of a piece of nerve, measuring approximately 1.4 cm. in length, with two branches, each about 1 cm. long. The main portion of the

Fig. 3.—Nerve bundle in another neuroma of Morton's metatarsalgia. Features are similar to those in Figure 2, but without the perineural fibrous nodule. The intrafascicular hyaline arteriolosclerosis is seen in greater detail. Hematoxylin and eosin stain; reduced to 59% of mag. × 102.

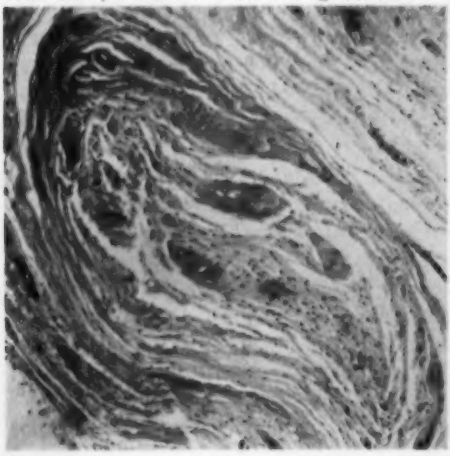


Fig. 4.—Several nerve bundles in a plantar digital neuroma with practically complete replacement by dense, hyalinized connective tissue. Some nerve fibrils are still identifiable in the two smaller bundles. Hematoxylin and eosin stain; reduced to 59% of mag. × 57.

nerve was affected by a fusiform swelling, and in one case the swelling extended into one of the branches. In the other cases from the files of Jackson Memorial Hospital and the Armed Forces Institute of Pathology a swelling of the nerve was indicated in the description by the pathologist or in the surgical note.

The microscopic features were distinctive. The principal findings were intraneural and interfascicular edema; fibrosis with subsequent hyalinization of the perineurium, together with interfascicular and intrafascicular fibrosis, and intrafascicular neural degenerative changes, such as demyelination and actual diminution of nerve fibers (Fig. 1). The latter was so pronounced at times that the nerve bundles had a "washed-out" appearance (Figs. 2 and 3). The interfascicular edema and fibrosis caused a prominent separation of the nerve bundles (Fig. 1). In one instance there was a large nodule of dense, hyalinized fibrous tissue arising from the perineurium of a large bundle, which compressed the latter (Fig. 2). This nodule was not a fibroma, although it was superficially suggestive of it. In another specimen several of the nerve bundles were practically completely replaced by hyalinized fibrous tissue (Fig. 4).

There was no consistent correlation between the degree of changes and the duration of symptoms. What might be regarded as an early lesion was seen in the specimen removed only a "few weeks" after onset of symptoms, i. e., interfascicular and intrafascicular edema without much fibrosis or neural degeneration. However, the same picture was seen in one case in which the duration of symptoms was 10 months. Yet in another, in which symptoms existed for three months, advanced changes were observed, characterized by marked fibrosis, hyalinization, and neural degeneration, and the lesion resembled one obtained from a patient who had symptoms for 10 years. In the specimen with the fibroma-like nodule, advanced changes were also evident. The patient from whom this was removed had symptoms for three years. The specimen with practically complete replacement of several of the nerve bundles by hyalinized fibrous tissue was removed from a patient who had symptoms about one year.

Proliferation of histiocytes, together with young fibroblasts, was seen in two specimens, associated with marked edema. These are most likely evidence of a reparative process. But no infiltration by other forms of inflammatory cells was observed. In more than a third of the cases fibrin was present in the lesion (Fig. 1). It was seen lining a bursa, which was sometimes included with the specimen, or it was present in the adjacent connective tissue. Neither fresh hemorrhage nor hemosiderin pigment, suggesting previous hemorrhage, was present.

Vascular changes were also evident. Interfascicular vessels were frequently prominent and even appeared increased in number (Fig. 1). The walls of the interfascicular arterioles were sometimes thickened. The intrafascicular arterioles were also prominent, and their walls were often thickened and hyalinized, a feature which was particularly striking in the cases with obvious neural degeneration and loss of nerve fibers. The appearance of the arteriolar change was similar to that seen in the hyaline form of arteriolosclerosis associated with so-called benign hypertension (Figs. 1-3). In more than a third of the cases a section of the digital artery was observed. In each one there was a marked proliferation of the intima but no inflammatory cells in the wall (Figs. 5 and 6). In one instance the narrowed lumen contained a small, fresh thrombus (Fig. 6). It is interesting to observe that the ages of the patients with the endarterial changes varied from 20 to 34 years. Except for the usual reactions of connective tissue to the periodic acid-Schiff and toluidine blue stains, no specific changes were demonstrated by these techniques. No amyloid was identified.

Comment

As we have seen in the published reports and in the present series of cases, the clin-

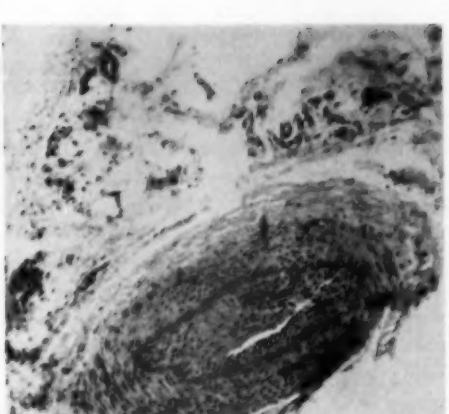
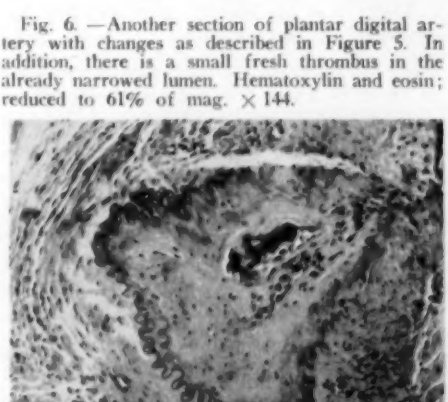


Fig. 5.—Section of plantar digital artery in case of Morton's metatarsalgia, showing marked intimal proliferation and narrowing of the lumen. Hematoxylin and eosin stain; reduced to 59% of mag. × 144.

ical picture of Morton's metatarsalgia is a very characteristic one. It would appear from the present study that the disease occurs only slightly more frequently in women than in men (10:7), but other reports in the literature indicate that the disease is much more prevalent in women. It was interesting to observe that in only 1 of the 17 patients was the condition bilateral. This is in agreement with most other studies that the disease is usually unilateral. However, in these reports, one gets the impression that the percentage of bilateral involvement is considerably greater than in the present series. Conservative therapy, such as the use of arch supports or special shoes, gives some relief for a time to patients with this disease. But permanent cure is obtained by operative therapy, i. e., by removal of the affected portion of the plantar digital nerve.

Nature of Lesion.—Much attention has been given to the nature of the lesion of Morton's toe and to its pathogenesis. It is quite well established that the principal change is in one of the plantar digital nerves, most frequently the fourth. This is characterized grossly by a swelling of the nerve, commonly referred to as a "neuroma." The term neuroma, however, is not used in the sense of a true neoplasm. Reference has been made to the associated proliferation of neurilemmal nuclei in some specimens,[1] but generally proliferation of nerve structures is not a striking feature of this lesion. In McElvenny's report,[11] it is implied that the lesion is a neoplasm, for he stated that specimens which were studied microscopically appeared to be either "neurofibromata" or "angioneuromata." Unfortunately, he did not give a detailed description of the lesions, nor did he include photomicrographs in his report, so that it is not possible to determine the histologic basis for his interpretation. In this connection, it is interesting to note that the lesions in 5 of the 17 cases of my series were diagnosed as "neurofibroma," "plexiform neurofibroma," or "neurinoma" by pathologists who first received the specimens in their laboratories. The plantar digital neuroma differs from the usual "traumatic or amputation neuroma," which consists of a coiled mass of proliferating nerve fibers, nerve sheaths, and fibrous tissue. The lesion of Morton's toe is characterized by edema, fibrosis, and nerve degeneration. Perhaps the designation "neuroma" is not

Fig. 6.—Another section of plantar digital artery with changes as described in Figure 5. In addition, there is a small fresh thrombus in the already narrowed lumen. Hematoxylin and eosin; reduced to 61% of mag. × 144.



the best one, but, because of its traditional use, it is difficult to replace the term even if a more suitable one could be found. The term suggested by King,[12] "sclerosing neuroma," has some merit in that it emphasizes a principal feature, namely, the overabundance of fibrous tissue, which tends to undergo hyalinization.

The condition is also described as "plantar digital neuritis," probably because the lesion is regarded as a reaction to some form of irritation, and not because there is an associated inflammatory reaction. The latter has not been described in the reported cases. In the present series, except for the histiocytes seen in the two cases with marked edema and fibroblastic proliferation, no other inflammatory cells were observed. Fibrin was seen, in some of the specimens, on the inner lining of the bursae and in the adjacent connective tissue. The fibrinous exudate probably resulted from the existing physical irritation rather than from the operative procedure. Reference to bursal involvement in this disease was also made by Mulder,[14] who observed that the neuroma became intimately connected with the plantar wall of the bursa, so that it could not be removed without opening the bursa. He found evidence of frequent damage to the bursal wall, as indicated by fibrous thickening of it; but he did not describe acute, fibrinous exudate. Just how much the involvement of the bursa contributes to the clinical picture is not determined.

The vascular changes are of considerable interest. It appears that there is an increase of vascularization in the interfascicular zones. The marked thickening and hyaline appearance of the walls of the intrafascicular arterioles in some of the cases (i. e., a hyaline arteriolosclerosis) are striking and characteristic features. The changes in the digital arteries are similar to those that Ringertz and Unander-Scharin[7] described. They referred to the lesion as "endarteritis," but, as in the cases of the present series, no inflammation was observed. Nissen[2] strongly emphasized that degenerative vascular lesions of the digital arteries were an essential part of this entity. It is important to recognize that the lesion of the digital artery is a local one, and it is not to be confused with more widespread vascular disease, such as thromboangiitis obliterans.

Pathogenesis.—In the pathogenesis of the disease, trauma from weight bearing and from use of small, high-heeled or other ill-fitting shoes is regarded as being significant. The probable association with high-heeled shoes may be one reason that the condition is more prevalent among women. Stretching of the nerve is probably a very important factor contributing to the development of the nerve lesion. The anatomic considerations emphasized by Betts[10] concerning the double derivation of the fourth plantar digital nerve and its lessened mobility are responsible for the greater degree of stretching in that nerve during dorsiflexion of the foot and toes, especially in walking.

It is recognized that the double origin of this nerve is not always evident, and that sometimes plantar neuromas occur in the other digital nerves. Therefore, other local factors contributing to the irritation must be considered. Some evidence that stretching may be significant is obtained from the observation of similar changes in other nerves under traction. Lyons and Woodhall,[16] in their studies of "neuroma in continuity," describe one form of "traction," or "stretch," fibrosis, the type unassociated with rupture of the nerve, which resembles the changes seen in the lesion of Morton's toe, in my opinion.

Nissen[2] indicated that the most likely factor in the pathogenesis of the lesion in Morton's metatarsalgia was repeated minor trauma through the sole, but he believed that the primary lesion was vascular degeneration, which subsequently caused ischemic changes of the nerve. He referred to similar lesions occurring "on the median and ulnar nerves in certain late cases of Volkmann's contracture where the nerve lesions

are undoubtedly secondary to ischaemia." Ringertz and Unander-Scharin [7] have shown that "chronic endarteritis" is a frequent phenomenon in Morton's disease, but they also observed that "endarteritis" of this type occurred almost as frequently in control material. They did not deny that the vascular change was responsible for the fibrosis, but they were of the opinion that "in most cases it does not give rise to any painful symptoms."

In addition to the evidence seen in cases of Volkmann's contracture, lending support to Nissen's hypothesis, there are observations in the literature on patients with peripheral vascular disease concerning the effect of ischemia on peripheral nerves. It is generally felt that the excruciating pain which is characteristic of thromboangiitis obliterans is the result of ischemia of the nerves due to occlusion of the vessels supplying the nerves. Barker,[17] in his cases of thromboangiitis obliterans, reported that ischemia was also responsible for certain anatomic changes in peripheral nerves, such as perineural and intrafascicular fibrosis, partial demyelination, edema, and atrophy of nerve fibers. It should be noted, however, that in a previous study by Meleney and Miller [18] these findings were not demonstrated. These authors paid particular attention to the main arteries of the big nerves in their patients with thromboangiitis obliterans. In almost half of the cases there was complete occlusion of these nutrient vessels, while a few showed mural thrombi. The authors made a number of examinations to demonstrate nerve degeneration, but they found "no absence of axis cylinders and no destruction of myelin sheaths." They commented that this was "interesting in view of the delicacy of nervous tissue in the cord and the rapidity with which a cutting of the blood supply will cause a degeneration of the central nervous tissue." A possibility which may be considered in order to explain the lack of nerve changes observed by these authors is that the collateral circulation in their cases was efficient. The importance of the anastomosis, on and within peripheral nerves, between nutrient arteries derived from different major arteries is emphasized in the studies by Sunderland.[19]

Denny-Brown and Brenner,[20] by means of a spring clip, exerted pressure on the sciatic nerve of animals and produced changes in the nerve, depending on the degree and duration of tension applied. Even with transient pressure, edema of the nerve and loss of myelin were observed in the compressed areas which persisted for as long as six to eight weeks. With continuous compression, edema and degeneration of the nerve above and below the point of pressure were produced. The authors attributed the effect of pressure on the nerve entirely to ischemia. In subsequent experiments, Denny-Brown and Doherty [21] produced lesions in the peroneal nerve by varying degrees of stretching of the nerve. In one experiment they produced neural edema and degeneration, with thickening of the perineurium and fibroblastic proliferation of the epineurium in some areas. In some arterioles, the walls were thickened and there was a proliferation of the intima with occasional thrombosis of a small artery. The nerve changes were considered to be the result of ischemia. With severer stretching neuromas were produced. They claimed that this resulted from herniation of nerve fibers through the perineurium. The fibers at the point of swelling, and for a distance on either side, underwent necrosis. This change, they felt, was probably the result of related vascular damage. The endoneural fibroblastic tissue then proliferated, resulting in the neuroma.

Thus, there appears to be sufficient support in the literature for the hypothesis of Nissen that the neural degeneration and subsequent fibrosis in Morton's disease are the result of ischemia. The most likely initiating factor in the development of the nerve lesion is physical irritation in the form of pressure on, or, more particularly, stretching of, the plantar digital nerve. That the trauma, in itself, may cause direct dam-

age to the nerve cannot be excluded; but it is more likely that the trauma produces the major damage, if not all, by the development of varying degrees of ischemia. In the beginning of the disease, ischemia is perhaps caused by vasospasm and/or compression of the vessels produced by pressure on, or stretching of, the nerve. As the disease progresses, the induced endarterial change in the digital artery and the intrafascicular arteriolar lesions probably contribute to the ischemia. The factors of vasospasm and compression of the vessels may be superimposed periodically upon the anatomic vascular changes during the entire course of the disease. It would seem that the severity of changes in the nerve lesion is dependent upon the degree of intensity of the injurious factors, including the initiating trauma and the resulting ischemia, and is not necessarily related to the duration of the symptoms.

It is difficult to give an adequate explanation of the exact mechanism of the production of pain in patients with Morton's metatarsalgia. Unfortunately, the cutaneous nerve endings were not studied in the cases with this entity, so that nothing can be said about the state of these structures. Ringertz and Unander-Scharin[7] concluded, "Some special factors, so far unknown, and possibly connected with endarteritis or fibrosis, must be presumed for the appearance of the pain complex." Because of the high incidence of intraneural edema and demyelination in cases of Morton's toe, they suggested that the pain may be connected in some way "with some specially accentuated disturbance of the circulation or metabolism of the nerves." White and Sweet,[22] in discussing the mechanism of pain in traumatic or amputation neuromas of the peripheral nerves, refer to the possible role of anoxia, either from local scarring or from widespread vasoconstriction. They cite investigative studies showing that a nerve which has been made anoxic will fire off repetitive stimuli, suggesting that impaired circulation may be a fundamental source of painful stimuli. Other studies which they cite suggest that certain hypothetical metabolites liberated at a point of nerve injury may contribute to the production of pain. In addition to these, another possible factor to which they make reference, particularly in regard to the production of such sensations as burning pain experienced in nerve injuries, is direct cross stimulation of sensory fibers by efferent sympathetic impulses at a point where the nerve trunk is injured.

It is possible, then, that in Morton's metatarsalgia ischemia does play a role in the production of pain through the mechanisms suggested in the preceding paragraph. The ischemia that exists because of the anatomic changes of the digital artery and the intrafascicular arterioles may make the injured nerves more sensitive to pain stimuli. The actual cause of the pain may be an intensification of the ischemia by vasospasm or compression of the vessels produced by one or both of the physical irritating factors, pressure and stretching. The possibility that these physical factors act directly on the already injured nerve fibers in producing the pain must also be considered. The relief obtained by resting or by removal of the shoe apparently is due to the temporary elimination of these factors.

Summary

The typical syndrome referred to as "Morton's toe" or "Morton's metatarsalgia" is discussed. Pertinent literature is reviewed which covers the development of our knowledge concerning the subject. The clinical and pathologic features of 17 cases of this entity are presented.

The syndrome occurs more frequently in women and is characterized by neuralgic pain in the foot, usually beneath the heads of the third and fourth metatarsals. The initiating cause of the disease is thought to be trauma from weight bearing, and from the use of small, high-heeled or other ill-fitting shoes. The symptoms are associated with a lesion of the plantar digital nerve, usually the fourth, which is commonly referred to as a neuroma. The nature and

pathogenesis of this lesion are discussed at length.

Therapy of this disease consists of a trial of conservative measures, such as the use of arch supports and special shoes, but curative therapy is considered to be surgical removal of the affected portion of the plantar digital nerve.

Capt. W. M. Silliphant (MC), U. S. N., Director of the Armed Forces Institute of Pathology, permitted use of material from the files of the Institute for this study, and Mr. William Atkinson made the photomicrographs.

University of Miami School of Medicine.

REFERENCES

1. Bickel, W. H., and Dockerty, M. B.: Plantar Neuromas, Morton's Toe, Surg. Gynec. & Obst. 84:111-116, 1947.

2. Nissen, K. I.: Plantar Digital Neuritis: Morton's Metatarsalgia, J. Bone & Joint Surg. 30-B:84-94, 1948.

3. Morton, T. G.: A Peculiar and Painful Affection of the Fourth Metatarso-Phalangeal Articulation, Am. J. M. Sc. 71:37-45, 1876.

4. Pincus, A.: Intractable Morton's Toe (Neuroma): Review of the Literature and Report of Cases, J. Nat. A. Chiropodists 40:19-35 (Dec.) 1950.

5. Durlacher, L.: A Treatise on Corns, Bunions, the Disease of Nails and the General Management of the Feet, London, Simpkin, Marshall & Co., 1845, p. 52.

6. Morton, T. S. K.: Metatarsalgia (Morton's Painful Affection of the Foot), Am. J. Surg. & Gynec. 3:204-208, 1892.

7. Ringertz, N., and Unander-Scharin, L.: Morton's Disease: A Clinical and Patho-Anatomical Study, Acta orthop. scandinav. 19:327-348, 1950.

8. Morton, D. J.: The Human Foot: Its Evolution, Physiology and Functional Disorders, New York, Columbia University Press, 1935, pp. 184 and 211.

9. Lewin, P.: The Foot and Ankle: Their Injuries, Diseases, Deformities and Disabilities, Ed. 2, Philadelphia, Lea & Febiger, 1941, pp. 170-176.

10. Betts, L. O.: Morton's Metatarsalgia: Neuritis of the Fourth Digital Nerve, M. J. Australia 1:514-515, 1940.

11. McElvenny, R. T.: Etiology and Surgical Treatment of Intractable Pain About the Fourth Metatarso-Phalangeal Articulation (Morton's Toe), J. Bone & Joint Surg. 25:675-679, 1943.

12. King, L.: Note on the Pathology of Morton's Metatarsalgia, Am. J. Clin. Path. 16:124-128, 1946.

13. Winkler, H.; Feltner, J. B., and Kimmelstiel, P.: Morton's Metatarsalgia, J. Bone & Joint Surg. 30-A:496-500, 1948.

14. Mulder, J. D.: The Causative Mechanism in Morton's Metatarsalgia, J. Bone & Joint Surg. 33-B:94-95, 1951.

15. Nissen, K. I.: Etiology of Morton's Metatarsalgia, Correspondence, J. Bone & Joint Surg. 33-B:293-294, 1951.

16. Lyons, W. R., and Woodhall, B.: Atlas of Peripheral Nerve Injuries, Philadelphia, W. B. Saunders Company, 1949, pp. 189 ff.

17. Barker, N. W.: Lesions of Peripheral Nerves in Thromboangiitis Obliterans: A Clinicopathologic Study, Arch. Int. Med. 62:271-284, 1938.

18. Meleney, F. L., and Miller, G. G.: A Contribution to the Study of Thrombo-Angiitis Obliterans, Ann. Surg. 81:976-993, 1925.

19. Sunderland, S.: Blood Supply of Peripheral Nerves: Practical Considerations, Arch. Neurol. & Psychiat. 54:280-282, 1945.

20. Denny-Brown, D., and Brenner, C.: Lesion in Peripheral Nerve Resulting from Compression by Spring Clip, Arch. Neurol. & Psychiat. 52:1-19, 1944.

21. Denny-Brown, D., and Doherty, M. M.: Effects of Transient Stretching of Peripheral Nerve, Arch. Neurol. & Psychiat. 54:116-129, 1945.

22. White, J. C., and Sweet, W. H.: Pain: Its Mechanisms and Neurological Control, Springfield, Ill., Charles C Thomas, Publisher, 1955, pp. 362-363.

designed for the professional...

LEITZ ***LABOLUX*** MICROSCOPE

Scientists, physicians and technicians who must work for long periods with a microscope will appreciate the new Leitz LABOLUX with its *fatigue-free operation, precision optics and unexcelled dependability.*

- Stage—instead of tube—moves for focusing.
- Individual coarse and fine adjustments are combined in a single, clutch-operated control knob.
- All controls including those for the mechanical stage in low position for fatigue-free operation.
- Can be used facing away from observer, for greater accessibility of all controls.
- Pre-aligned substage illuminator or mirror.
- Retractable spring mounts in objectives prevent damage to lens and slides.
- Inclined binocular body tube interchangeable with monocular tube for photomicrography.

Send for ***LABOLUX*** brochure *today.*

See and examine the new Leitz ***LABOLUX*** microscope *soon.*

E. LEITZ, INC., 468 FOURTH AVENUE, NEW YORK 16, N. Y.
Distributors of the world-famous products of Ernst Leitz, Wetzlar, Germany
LENSES • CAMERAS • MICROSCOPES • BINOCULARS

E. Leitz, Inc., Dept. AP-1
468 Fourth Ave., New York 16, N. Y.

Please send me your brochure on the new Leitz **LABOLUX.**

Name _____

Street _____

City _____ State _____

the versatile
"ready-to-use" control

LAB-TROL® by DADE

SO INEXPENSIVE it can be used daily with *each run of a test procedure.*

For positive assurance of accuracy in blood chemistries. Lab-Trol comes in liquid form, ready to use from the bottle. Treated like serum or whole blood, it goes through every step of a procedure including protein precipitation. For daily checks on the accuracy of tests, technique, instruments and reagents, run Lab-Trol in parallel with unknown samples.

Lab-Trol remains stable indefinitely, and because it is ready to use, is not subject to dilution errors. For tests with antigens, Lab-Trol contains human syphilis reagin (antibody)—gives 4+ reaction.

EACH VIAL OF LAB-TROL will serve as a standard for all the following procedures:

- Total Protein
- Glucose
- Magnesium
- Blood Urea Nitrogen
- Creatinine
- Phosphorus—inorganic
- Non-Protein Nitrogen
- Sodium
- Potassium
- Calcium—total
- Chlorides (as NaCl)

No. 53455—Lab-Trol, package of six 3.5 ml. vials per package $9.00

You can rely on Scientific Products—

Ainsworth balances
American Optical microscopes
B.B.L. culture media
Barnstead stills
Bausch & Lomb microscopes
Beck Lee E.K.G. equipment
Beckman instruments
Becton-Dickinson equipment
Berkeley radioisotope equipment
Browne-Morse sectional cabinetry
Christian Becker balances
Clay Adams medical equipment
Coleman spectrophotometers
Coors porcelain
Corning glass
Dade serums
DiSPo items—disposable specialties
Hartman-Leddon chemicals
Hycel clinical testing equipment
International centrifuges
Jewett refrigerators
Kimble glassware
Labline laboratory equipment
Lindberg hotplates & furnaces
Lipshaw tissue equipment
Mallinckrodt reagent chemicals
Matheson Coleman & Bell organic chemicals
Monaghan respiratory equipment
Ohaus scales
Precision scientific equipment
Schieffelin pharmaceuticals
SP laboratory specialties
Spinco electrophoresis apparatus
Sylvana serological reagents
Torsion balances
Virtis virus & tissue equipment
Warner-Chilcott pharmaceuticals

No matter what your laboratory needs—be sure to consult your SP representative first!

SP **Scientific Products**

DIVISION OF AMERICAN HOSPITAL SUPPLY CORPORATION

New York • Chicago • Kansas City • Minneapolis • Atlanta • Washington • Dallas • Los Angeles • San Francisco

Would Ben Franklin have settled for less than PYREX®?

Dr. Franklin had a simple but effective method for wringing the last drop of buying power out of a budget dollar.

He wrote down all the advantages and disadvantages of taking a certain action. With all the facts in front of him, he was sure to make the right decision.

Should Dr. Franklin be buying labware today, his list on PYREX brand might well look like this:

Advantages of PYREX labware

1. Less, much less, breakage. Shows heavier construction, especially at joints, lips, and other stress points. Next two properties save breakage too.

2. Takes heat, sudden temperature changes. I can subject this glassware to sudden temperature changes without damaging it. Its coefficient of expansion is only 0.0000033 per ° C. between 0° and 300° C.

3. Chemically stable. PYREX brand labware resists almost all common acids and alkalies.

4. No contamination. Contains no elements of the magnesia-lime-zinc group. No heavy metals. Low alkali content. Result: No contamination of contents even over long storage periods.

5. Complete line. Having all glassware made of exactly the same glass gives me better test control. I can get all the different glassware I'll ever need with this PYREX.

Disadvantages

1. On some items PYREX brand labware costs a bit more. However, in terms of value and breakage, I can actually save money over the long run.

2. Some reagents—hot HF, for example—do affect this (as well as other) glasses. But it's perfectly adequate for about 99.9% of my work.

Conclusion: Dollar for dollar, I'll get more for my money if I look for this trademark PYREX whenever I buy glassware.

Try it yourself. Make your own "advantage-disadvantage" list on PYREX brand labware. Might make your dollars work harder too.

Might be easier if you use our Standard Labware Catalog LP36 and our Special Apparatus Catalog CA-2. Send for copies.

CORNING GLASS WORKS
87-1 Crystal Street, Corning, N. Y.
Corning means research in Glass

PYREX®

PYREX® laboratory ware

. . . the tested tool of modern research

Now! Convert "water colors" to "oils" in your laboratory

In colorimetric blood chemistry methods, aqueous standards can be misleading. Versatol makes available—for the first time—a *known,* multiple blood chemistry standard in whole human serum, permitting an easier, more precise matching of colors. This preparation duplicates all the interfering substances in the patient's serum, including lipids, and checks all the procedures necessary in the testing.

At last—a control for PBI. Versatol contains a much-needed control for serum protein-bound iodine. Now, this important, delicate test can be run without fear of *undetected* contamination. In addition, Versatol includes a known normal concentration of: total nitrogen . . . total protein . . . nonprotein nitrogen . . . urea nitrogen . . . creatinine . . . sodium . . . potassium . . . chlorides . . . phosphates . . . calcium . . . glucose.

Simple to use: Versatol is ready for use with just the addition of distilled water, thus eliminating the tedious task of preparing innumerable solutions. No further manipulations are necessary.

Available from leading local laboratory supply distributors in boxes of ten 5-ml. vials, $21.00.

Versatol

TRADEMARK

WARNER-CHILCOTT

Laboratory Supply Division, Morris Plains, New Jersey

the new Autotechnicon® takes a third less space has 20% more capacity

actual size on 10 foot bench

From the very beginning . . . in the very first Autotechnicon which introduced automation to tissue-processing . . . a round deck was used because only in a circle can you condense so many beakers, so compactly. It's simple geometry.

But even the best idea can be improved, the deck is still a perfect circle . . . but it is smaller by a third. Still, the new radial beakers have 20% more capacity of both fluid and tissues than the previous ones.

Since it doesn't sprawl all over the place, as you see above, the New Autotechnicon, occupies only the very corner of your lab-bench, leaving almost the entire bench free and clear for other work.

the entire Autotechnicon is mounted on a free-wheeling quiet turntable . . . just rotate it to bring any beaker to the front

Write today for Booklet 2-AT, for description of these new instruments.

the Autotechnicon®

Trailblazer in histologic automation

THE TECHNICON COMPANY

Chauncey New York